STUDY OF DRUG INDUCED-SKIN REACTIONS IN THE PATIENTS ATTENDING OUTPATIENT DEPARTMENT OF DERMATOLOGY

Dissertation submitted to

The Tamilnadu Dr. MGR Medical University

In partial fulfillment of the regulations for

The Award of the Degree of

M.D. PHARMACOLOGY

BRANCH - VI

DEPARTMENT OF PHARMACOLOGY

KILPAUK MEDICAL COLLEGE

CHENNAI – 600 010.

OCTOBER - 2015

CERTIFICATE

This to certify that the dissertation entitled **"STUDY OF DRUG INDUCED-SKIN REACTIONS IN THE PATIENTS ATTENDING OUTPATIENT DEPARTMENT OF DERMATOLOGY**" by the candidate **Dr. A. MEERADEVI Regn. No. 20112781** for **M.D PHARMACOLOGY (Branch VI)** is a bonafide record of the research done by her during the period of study **(2011 -2015)** in the Department of Pharmacology, Kilpauk Medical College, Chennai – 600010.

Dr. R. Narayana Babu, M.D (Pead)
Dean,
Kilpauk Medical College,
Chennai – 10

Date :

Station :

Dr. C. Ramachandra Bhat, M.D
Professor & Head and Guide
Department of Pharmacology,
Kilpauk Medical College,
Chennai – 10

Date :

Station :

DECLARATION

I solemnly declare that this dissertation entitled **"Study of drug induced-skin reactions in the patients attending outpatient department of dermatology"** was written by me in the Department of Pharmacology, Kilpauk Medical College, Chennai, under the guidance and supervision of **Prof. Dr. C. Ramachandra Bhat, M.D.,** Professor and Head, Department of Pharmacology, Kilpauk Medical College, Chennai – 600 010.

This dissertation is submitted to **THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY** Chennai, in partial fulfillment of the university regulations for the award of **DEGREE OF M.D PHARMACOLOGY (BRANCH - VI)** examinations to be held in **OCTOBER – 2015.**

Date :

Place : Chennai **Dr. A. MEERADEVI**

ACKNOWLEDGEMENT

“Gratitude is the humble gift; I can give to my beloved Teachers”.

I express my profound gratitude to the **Dean, Dr. R. Narayana Babu, M.D.,** Kilpauk Medical College and Hospital, Chennai for granting me permission to conduct the study at the Department of Pharmacology and Dermatology, Kilpauk Medical College.

I thank my respectful **Prof. Dr.C. Ramachandra Bhat, M.D., HOD**, Department of Pharmacology, Kilpauk Medical College, for having been very much supportive and encouraging for conducting this study.

I express my thanks to **Prof. Dr. Malar Sivaraman, M.D, Prof. Dr. T. Aruna, M.D.,** for their valuable help and suggestion throughout my study.

I express my thanks to **Prof. Dr.Vijay Anand M.D.D.VL.,** Head, Department of Dermatology, Kilpauk Medical College and Hospital, Chennai, and **Dr. A. Krishnaveni M.D.D.VL.,** Assistant surgeon, Department of Dermatology, Kilpauk Medical College and Hospital, Chennai for their valuable help and suggestion throughout my study.

I also express my thanks to **Assistant Professors Dr.G. Sasikala M.D., Dr. G. Komathi M.D., Dr. Jeya ponmari M.D.,** Department of pharmacology for their valuable help and suggestions throughout my study.

I am very much thankful to **Dr. Manimegalai M.D. Derm, Dr. B. T. Priya M.D.D.VL.,** Assistant Professor, and Department of Dermatology, kilpauk Medical College, Chennai and Hospital. I also thank **Dr. Ravananan,** statistician for guiding me in the biostatistics.

I also thank Tutors **Dr. Valamathi,** and **Dr. Subbulakshmi** for their help in this study.

I also thank my co-postgraduates **Dr. R. Taruni, Dr. Divya John Stephy, Dr. P. Priya** for their support and enthusiasm.

I thank our department Lab technician **Mrs. Alwar** for her help and support.

I sincerely thank my family members who have been my moral strength and support and for providing constant encouragement throughout my entire endeavor.

I also sincerely thank my patients, subjects, lab technicians and attender for their co-operation.

I thank the Almighty for giving me good health and blessings throughout the phase of this study.

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.8885/E1 (Ethics)/2011 Dt:06.09.2011 (Date of Meeting)
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "Study of Drug induced – skin reactions in the patients attending outpatient Department of Dermatology submitted by Dr.A. Meeradevi, MD (Pharmacology), PG Student, GKMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
29 APR 2015
Kilpauk, Chennai-10.

29/4/15

for CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

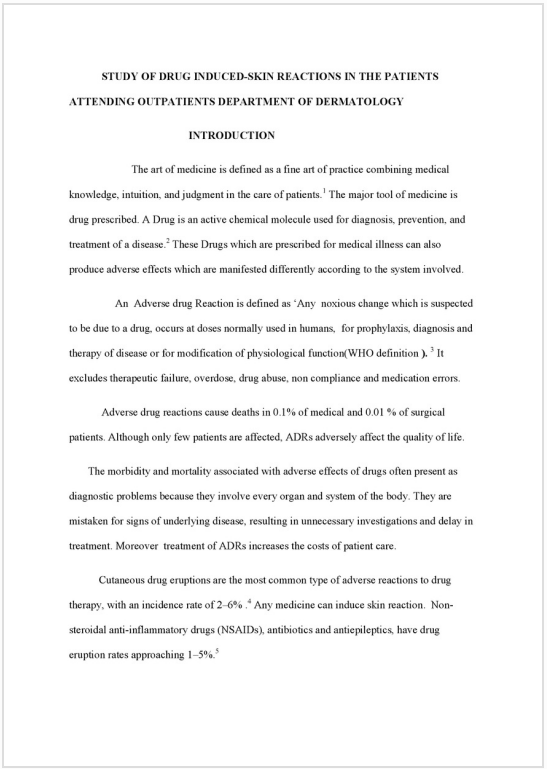
29/4/2015

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	20112781 .m.d.pharmacology Dr.A.M.
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	STUDY OF DRUG INDUCED-SKIN …
File name:	Plagiarism_Dr_Meeradevi.docx
File size:	200.96K
Page count:	80
Word count:	12,836
Character count:	77,807
Submission date:	29-Apr-2015 09:36AM
Submission ID:	535162364



STUDY OF DRUG INDUCED-SKIN REACTIONS IN THE PATIENTS ATTENDING OUTPATIENTS DEPARTMENT OF DERMATOLOGY

INTRODUCTION

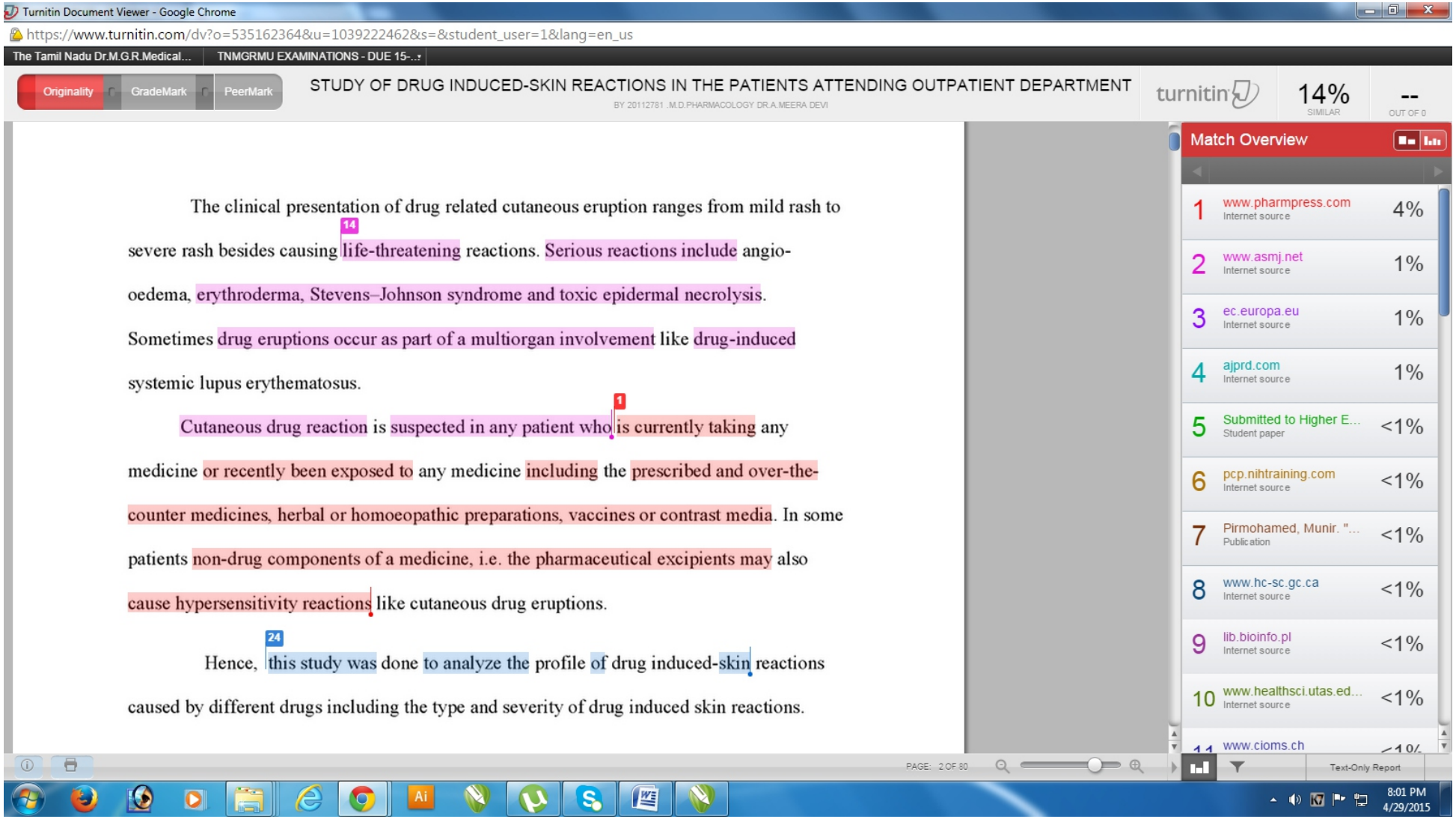
The art of medicine is defined as a fine art of practice combining medical knowledge, intuition, and judgment in the care of patients.[1] The major tool of medicine is drug prescribed. A Drug is an active chemical molecule used for diagnosis, prevention, and treatment of a disease.[2] These Drugs which are prescribed for medical illness can also produce adverse effects which are manifested differently according to the system involved.

An Adverse drug Reaction is defined as 'Any noxious change which is suspected to be due to a drug, occurs at doses normally used in humans, for prophylaxis, diagnosis and therapy of disease or for modification of physiological function(WHO definition).[3] It excludes therapeutic failure, overdose, drug abuse, non compliance and medication errors.

Adverse drug reactions cause deaths in 0.1% of medical and 0.01 % of surgical patients. Although only few patients are affected, ADRs adversely affect the quality of life.

The morbidity and mortality associated with adverse effects of drugs often present as diagnostic problems because they involve every organ and system of the body. They are mistaken for signs of underlying disease, resulting in unnecessary investigations and delay in treatment. Moreover treatment of ADRs increases the costs of patient care.

Cutaneous drug eruptions are the most common type of adverse reactions to drug therapy, with an incidence rate of 2–6% .[4] Any medicine can induce skin reaction. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1–5%.[5]


Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?o=535162364&u=1039222462&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 15-...
Originality
GradeMark
PeerMark
STUDY OF DRUG INDUCED-SKIN REACTIONS IN THE PATIENTS ATTENDING OUTPATIENT DEPARTMENT
BY 20112781 .M.D.PHARMACOLOGY DR.A.MEERA DEVI
turnitin
14%
SIMILAR
--
OUT OF 0
The clinical presentation of drug related cutaneous eruption ranges from mild rash to severe rash besides causing life-threatening reactions. Serious reactions include angio-oedema, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis. Sometimes drug eruptions occur as part of a multiorgan involvement like drug-induced systemic lupus erythematosus.
Cutaneous drug reaction is suspected in any patient who is currently taking any medicine or recently been exposed to any medicine including the prescribed and over-the-counter medicines, herbal or homoeopathic preparations, vaccines or contrast media. In some patients non-drug components of a medicine, i.e. the pharmaceutical excipients may also cause hypersensitivity reactions like cutaneous drug eruptions.
Hence, this study was done to analyze the profile of drug induced-skin reactions caused by different drugs including the type and severity of drug induced skin reactions.
Match Overview
1 www.pharmpress.com Internet source 4%
2 www.asmj.net Internet source 1%
3 ec.europa.eu Internet source 1%
4 ajprd.com Internet source 1%
5 Submitted to Higher E... Student paper <1%
6 pcp.nihtraining.com Internet source <1%
7 Pirmohamed, Munir. "... Publication <1%
8 www.hc-sc.gc.ca Internet source <1%
9 lib.bioinfo.pl Internet source <1%
10 www.healthsci.utas.ed... Internet source <1%
www.cioms.ch
PAGE: 2 OF 80
Text-Only Report
8:01 PM
4/29/2015

ABSTRACT

Title: Study of drug induced-skin reactions in the patients attending outpatient department of dermatology

Degree for which submitted	:	Doctor of Medicine (M.D) in Pharmacology.
Supervisor & Guide	:	Prof. Dr. C. Ramachandra Bhat, M.D.,
Department	:	Department of Pharmacology and Dermatology.
College	:	Kilpauk Medical College, Chennai.
University	:	The Tamilnadu Dr.MGR Medical University, Chennai.
Year	:	2011 -2015.

Adverse drug reaction is any noxious change which is suspected to be due to drug, occurs at doses normally used in humans for prophylaxis, diagnosis, therapy of disease or for modification of physiological function. Adverse drug reactions cause both morbidity and mortality. Drug induced skin reactions are the most common type of adverse drug reaction and clinical presentation varies. We investigated the profile of drug induced skin reactions in the patients attending outpatient department of Dermatology, Kilpauk Medical College and Hospital, from September 2011 to February 2013. Data

were recorded in WHO Suspected adverse reaction report form and analyzed statistically by Chi-square test. Causality and severity of adverse drug reaction were done. In conclusion, analyzing 100 ADRs men were more affected than female. Drug rash was the most common drug induced skin reaction. The suspected drug causing more reactions was Antibacterial agent. Hence ADR data base studies conducted across multiple centres provide early warning signals in preventing adverse drug reactions.

Keywords : ADR, WHO, CAUSALITY.

CONTENTS

S.NO	TITLE	PAGE NO.
1.	INTRODUCTION	1
2.	REVIEW OF LITERATURE	3
3.	AIM & OBJECTIVES	45
4.	MATERIALS & METHODS	46
5.	RESULTS	49
6.	DISCUSSION	80
7.	CONCLUSION	89
	BIBLIOGRAPHY	
	ANNEXURES	
	PICTURES	

ABBREVIATIONS

ADR	-	Adverse drug reaction
WHO	-	World health organization
UMC	-	Uppsala monitoring centre
TEN	-	Toxic epidermal necrolysis
SLE	-	Systemic lupus erythematosus
IL	-	Interleukin
NSAID	-	Non-steroidal anti inflammatory drugs
FDA	-	Food and drug administration
CIOMS	-	Council for international organization of medical sciences
ICH	-	International conference on harmonization
SUSAR	-	Suspected unexpected serious adverse reaction
SSAR	-	Suspected serious adverse reaction
Cyp	-	Cytochrome
MDR	-	Multidrug resistant
Pgp	-	P glycoprotein
ACE	-	Angiotensin converting enzyme
ARB	-	Angiotensin receptor blocker
HLA	-	Human leucoyte antigen
Ig	-	Immunoglobulin
LD	-	Lethal dose

PSUR	-	Periodic safety update report
PMS	-	Post marketing surveillance
GCP	-	Good clinical practice
ATN	-	Acute tubular necrosis
PPI	-	Proton pump inhibitors
RAST	-	Radio allergen absorbent skin test
EM	-	Erythema multiforme
SJS	-	Steven Johnson syndrome
HIV	-	Human immunodefiency virus
G-CSF	-	Granulocyte colony stimulating factor
OTC	-	Over the counter
MAOI	-	Monoamine oxidase inhibitor

INTRODUCTION

The art of medicine is defined as a fine art of practice combining medical knowledge, intuition, and judgment in the care of patients.[1] The major tool of medicine is drug prescribed. A drug is an active chemical molecule used for diagnosis, prevention, and treatment of a disease.[2] These drugs which are prescribed for medical illness can also produce adverse effects which are manifested differently according to the system involved.

An Adverse drug Reaction is defined as 'Any noxious change which is suspected to be due to a drug, occurs at doses normally used in humans, for prophylaxis, diagnosis and therapy of disease or for modification of physiological function (WHO definition**).**[3] It excludes therapeutic failure, overdose, drug abuse, non compliance and medication errors.

Adverse drug reactions cause death in 0.1% of medical and 0.01 % of surgical patients. Although only few patients are affected, ADRs adversely affect the quality of life.

The morbidity and mortality associated with adverse effects of drugs often present as diagnostic problems because they involve every organ and system of the body. They are mistaken for signs of underlying disease, resulting in unnecessary investigations and delay in treatment. Moreover treatment of ADRs increases the costs of patient care.

Cutaneous drug eruptions are the most common type of adverse reactions to drug therapy, with an incidence rate of 2–6% .[4] Any medicine can induce skin reaction. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1–5%.[5]

The clinical presentation of drug related cutaneous eruption ranges from mild rash to severe rash besides causing life-threatening reactions. Serious reactions include angio-oedema, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis. Sometimes drug eruptions occur as part of a multiorgan involvement like drug-induced systemic lupus erythematosus.

Cutaneous drug reaction is suspected in any patient who is currently taking any medicine or recently been exposed to any medicine including the prescribed and over-the-counter medicines, herbal or homoeopathic preparations, vaccines or contrast media. In some patients non-drug components of a medicine, i.e. the pharmaceutical excipients may also cause hypersensitivity reactions like cutaneous drug eruptions.

Hence, this study was done to analyze the profile of drug induced-skin reactions caused by different drugs including the type and severity of drug induced skin reactions.

REVIEW OF LITERATURE

HISTORY

A drug causes good as well as harmful effects. Public and Professional concerns about harmful effects of drug started in late 19th century. Committees and commissions were started in 1870 to 1890 to investigate sudden death due to chloroform anesthesia which later was found due the effect of chloroform sensitizing the myocardium to arrythmogenic effects of catecholamines.[6] In USA in 1937, 107 people died due to an elixir of sulfanilamide that contained solvent diethylene glycol, which led to the establishment of Food and Drug administration to impose quality criteria for drug manufacturing.

In 1961, Thalidomide disaster occurred in which 6000 -250000 offsprings were born with phocomelia .The incident was found to occur due to drug thalidomide which is a hypnotic taken by pregnant women in first trimester for morning sickness. [7, 8] The thalidomide incident led public outcry to all the institutions around the world of drug regulatory authorities to make necessary sophisticated approaches for preclinical testing and clinical evaluation of drugs before marketing, increased awareness of adverse effects of drugs and methods of detecting them. Hence in1968 International drug safety monitoring by WHO came as a collaborative effort by 10 countries.

The adverse reactions to widely prescribed drugs have serious impact on the society. Hence knowledge and efficient reporting forms the basis of Pharmacovigilance. The national Pharmacovigilance centres were established

after 1972 that work in collaboration with WHO collaborating centre for international drug monitoring in Uppsala, Sweden (The Uppsala Monitoring Centre).

The new legislations and qualitative requirements have led to the establishment of Council for International Organizations of Medical sciences (CIOMS) and International Conference on Harmonization (ICH) which is instrumental in the development of Pharmacovigilance worldwide.

In India drug safety monitoring was proposed in 1986. Adverse reaction monitoring system of 1986 consisted of 12 regional centres. In 1997 more efforts began, in cooperation with WHO Uppsala monitoring centre.

On 1st January 2005, the more ambitious National Pharmacovigilance Programme of India was launched with WHO support and World Bank funding. The implementation of Schedule Y has also added support to National pharmacovigilance, so that it is mandatory to report all adverse events including suspected unexpected serious adverse reactions from clinical trials.

Hence adverse drug reactions to widely prescribed drugs have serious impact on the society which has to be researched.

EPIDEMIOLOGY

10-20 % of patients admitted in the hospital suffer from an adverse drug reaction. In the hospital 0.24-2.9 % deaths are due to adverse drug reaction.[9] 2-6% of hospital admissions are due to adverse drug reaction.[10-12] In England a

study was conducted which showed that more than 40 % of patients undergoing drug therapy are upset by their treatment[13] due to drug reaction.

Cutaneous drug eruptions are the most common type of ADR with incidence of about 2-5%. 75% to 95 % of cutaneous drug eruption are maculopapular rash/drug rash followed by utricaria.[14] 20% of emergency room visits for adverse event are due to antibiotics and nonsteroidal anti-inflammatory drugs which causes reaction of about 1 in 2000.[15].The reaction rate for digoxin, lidocaine, prednisolone, codeine are less than 1 in 1000.

ADR RISK FACTORS

Age (children and elderly), gender, multiple medications, multiple co-morbid conditions, inappropriate medications that were prescribed and used, improper monitoring, end-organ dysfunction, altered physiology, prior history of ADR's, extent (dose) and duration of exposure, genetic predisposition are the various risk factors.

Adverse drug reactions are more common in elderly due to changed pharmacokinetics and pharmacodynamics through organ failure, concomitant disease and drug interactions.

CLASSIFICATION OF ADVERSE DRUG REACTION

Adverse drug reaction is classified into many types according to dose, severity, type of effect, time, frequency and causality.

A) Classification based on dose relationship [16]

1) Dose related: a) Pharmaceutical variation b) Pharmacokinetic variation –Pharmacogenetic variation, hepatic disease, renal disease, cardiac disease, thyroid disease, drug interactions. c) Pharmacodynamic variation - Hepatic disease, altered fluid and electrolyte balance, drug interactions.

2) Non-dose-related: a) Immunological reactions

b) Pseudoallergic reactions c) Pharmacogenetic variation.

3) Long term effects: a) Adaptive changes

b) Rebound phenomenon c) Other long term effects.

4) Delayed effects: a) Carcinogenesis

b) Effects concerned with reproduction-1) Impaired fertility 2) Teratogenesis - Adverse effects on the fetus during early pregnancy, late pregnancy 3) Adverse effects due to drugs in breast milk

B) Classification according to type of effects (Pharmacological classification[17])

S.No	Type	Type of effect	Definitions	Examples
1.	A	Augmented	Adverse effects that are known to occur from the pharmacology of drug and dose related .They are seldom fatal and are relatively common.	Hypoglycemia due to insulin injection, bradycardia due to Beta adreneoreceptor antagonists, hemorrhage due to anticoagulants
2.	B	Bizarre effects	Adverse effects that occur unpredictably and often have a high rate of morbidity. They are uncommon	Anaphylaxis due to penicillin, Acute hepatic necrosis due to halothane, bone marrow suppression by chloramphenicol.
3.	C	Chronic effects	Adverse effects that occur only during prolonged treatment and not with single dose.	Iatrogenic Cushing's syndrome with prednisolone, myofacial dystonia due to phenothiazines, colonic dysfunction with laxatives
4.	D	Delayed effects	Adverse effects that occur remote from treatment either in the children of treated patients or in patients themselves years after treatment.	Secondary cancers in patients treated with alkylating agents for Hodgkin's disease, craniofacial malformation in infants whose mothers have taken isotretinoin, clear cell carcinoma of vagina of female offspring of women who had diethylstilbestrol.
5	E	End of treatment effects	Adverse effects that occur when a drug is stopped especially when it is stopped suddenly(withdrawal effects)	Unstable angina after Beta adrenoreceptor antagonists are stopped suddenly, Adrenocortical insufficiency with glucocorticoids, withdrawal seizures with anticonvulsants.

C) Classification according to the severity[18]

1) Mild - Bothersome but requires no change in therapy.

2) Moderate-Requires change in therapy, additional treatment, hospitalization. Definite biochemical or structural changes occurs due to moderate involvement of vital organs.

3) Severe - Potentially life threatening, causing permanent damage. Definitely requiring hospitalization due to severe impairment of vital organs.

D) Classification according to Seriousness [19]

1) Suspected Unexpected Serious Adverse Reaction (SUSAR)

2) Suspected Serious Adverse Reaction (SSAR)

Both results in death, life threatening situations and require intervention to prevent permanent damage. Both may result in disability and also causes congenital anomalies.

E) Frequency classification

Report from CIOMS (Centre for international organization of medical sciences) working group III, Geneva 1995 [20]

1) Very common (Optional) : >10%

2) Common (Frequent) : >1% and ≤ 10%

3) Uncommon (Infrequent) : >0.1% and ≤ 1%

4) Rare : 0.01% and ≤ 0.1%

5) Very rare (Optional) : <0.01%

F) Reaction time classification

Reaction time is defined as the time between the last drug exposure and the appearance of the first symptoms.[21]

1) Acute : 0-60 Minutes (4.3 % of reactions)

2) Subacute : 1-24 Hours (86 % of reactions)

3) Chronic : day to several weeks (3.5% of reactions)

F) WHO Causality classification [22]

Term	Discription
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible(pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological(i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality ,with reasonable time relationship to drug intake • Could not be explained by the disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or Laboratory test abnormality with a time to drug intake that makes a relationship improbable(but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or Laboratory abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

MECHANISM OF ADVERSE DRUG REACTION

PHARMACEUTICAL VARIATION

Alteration in the drug quantity for systemic absorption or release of drug produces toxicity due to the influence of various factors, i.e., size of the particle in pharmaceutical preparation like tablet, capsule, injection, nature and quantity of excipients, materials used for coating. When an irritant drug come into prolonged contact with a small area of gastrointestinal tract it leads to gastric hemorrhage, ulceration and perforation e.g. potassium chloride tablets.[23]

PHARMACOKINETIC VARIATIONS

Alteration in absorption, distribution, metabolism and excretion of drug causes adverse reactions.

Absorption

It is the movement of unchanged drug from the site of administration to systemic circulation. The rate and extent of drug absorption affects the pharmacologic effect. Gastrointestinal intestinal system is mainly involved in absorption .Any motility changes alters absorption.

Distribution

The transfer of drug between blood and extravascular fluids and tissue is distribution. The factors which affect the extravascular distribution are physiochemical characteristics, blood flow to the region, tissue binding, binding to plasma protein and active transport.

Binding of drugs to the tissues gains wider importance in causing adverse reaction. Some examples of ADRs due to extravascular tissue binding are as follows:

1. Hepatotoxicity due to epoxides of halogenated hydrocarbons and paracetamol.[24]
2. Renal toxicity by metallothionins binding to heavy metals.
3. Interaction of melanin in skin with chloroquine and phenothiazines.
4. Yellow discoloration of teeth and bones due tetracycline in children.
5. Binding to DNA by cyclophosphamide, azathioprine leading to carcinogenesis.

Metabolism

The conversion of drug from one form to another is metabolism. Biotransformation is synonymous with metabolism. Organs involved are liver, gut, skin, lung, kidney, adrenals and placenta.

Liver is the major organ of metabolism. In the liver oxidation by Cytochrome P-450 group of isoenzymes plays an important role. Metabolism of oral anticoagulants, phenothiazines, tricyclic antidepressants, benzodiazepines, barbiturates, and isoniazid involves this route.

Different races shows differences in the metabolism. Acetylation of isoniazid is an example of Polymorphism. Slow acetylators presented with hepatotoxicity and fast acetylators presented with peripheral neuropathy as adverse effect. Another example is Warfarin. Genetic variation in the

metabolism of warfarin by CYP2C9 is seen which leads to hemorrhagic incidence of 8-26 per 100 patient years.[25]

The hepatic metabolism is reduced in any pathological condition like hepatitis, cirrhosis, obstructive jaundice and hepatic carcinoma. The blood flow to liver is reduced in congestive cardiac failure and Myocardial infarction which impairs the metabolism of drug like propanalol and lidocaine.

In renal diseases glycine conjugation of salicylates, vitamin D oxidation, procaine hydrolysis is affected. Glucuronidation is reduced in diabetes mellitus due low availability of Uridine diphospho glucuronic acid.

Elimination or excretion

The drug or metabolite is transferred irreversibly to external environment which leads to termination of action of the drug. Kidneys are the prime organs of excretion. Also bile, sweat, breast milk, lungs play minor role. Reduced elimination leads to toxic reaction. Nephrotoxic drugs are used with caution in renal impairment.

Drug interaction

Polytherapy leads to adverse drug reaction due drug interactions.[26] An Australian study showed that 4.4% of all adverse drug reactions resulting in hospital admission were due drug interactions.[27] The effect on metabolic pathway by drug interaction is due enzyme interaction or by enzyme inhibition.[28] Increased metabolism and drug clearance occurs due to enzyme induction which does not cause adverse drug reaction. On the other hand enzyme inhibition leads to decreased drug clearance leading to toxicity.

Examples:

1) Interaction between CYP3A4 inhibitors Ketoconazole and erythromycin and terfenadine.

2) P-Glycoprotein (Pgp) over expression leads to resistance of antitumor drugs. P-Glycoprotein is encoded by MDR1 gene.

3) Digoxin toxicity with quinidine, amiodarone due inhibition of Pgp.[29]

PHARMACODYNAMIC VARIATIONS

In general population pharmacodynamic variability is compounded by diseases of various systems. Hepatic diseases alter pharmacodynamic parameters leading to hemorrhage or peptic ulcer with Non-steroidal anti inflammatory drugs. Hepatic encephalopathy causes brain sensitization to sedatives leading to frank coma. Sodium and water retention occurs with drugs like NSAIDs, carbamazepine, carbenoxolone, and sodium salt of penicillin.

Bronchoconstriction in obstructive airway disease occurs when beta blockers are used. Aminoglycoside precipitates neuromuscular blockade in Myasthenia gravis. Hypokalemia precipitates arrhythmia with antiarrythmics such as quinidine, procainamide, and dysopyramide causing Torsade de pointes. Skeletal muscle relaxant – Tubocurarine's action is prolonged by Hypocalcaemia. Hypotensive effect of ACE inhibitors is enhanced by fluid depletion.

IMMUNOLOGICAL / ALLERGIC / HYPERSENSITIVITY REACTIONS

The drug and the patient are main factors in drug allergy.

Drug

Proteins, polypeptides, dextrans are immunogenic in nature. Haptens are smaller molecules that combine with body proteins and form antigens. Drugs or their metabolites act as haptens in immunological reactions.

Patient

Genetic factors play role in allergic reaction. In Atopic disease, eczema, asthma, hay fever, hereditary angioedema allergic reactions are more common.

HLA status

Human lymphocyte antigens are important for the function of T lymphocyte in stimulation by foreign antigens. HLA antigens are located on the short arm of chromosome 6. Nephrotoxicity due to pencillamine is increased in patients with HLA type B8 and DR3. Hydralazine associated Lupus like syndrome is seen in patients with HLA DR4.

TYPES OF HYPERSENSITIVITY REACTIONS (Stephen MBD et al, 1998)

Type 1 reaction (Anaphylaxis/Immediate hypersensitivity)

Reaction occurs when the drug or metabolite combines with antigen specific Ig E on mast cells and basophils leading to the formation of drug/antigen-specific IgE cross-links. Hence chemical mediators like histamine, kinins, 5-hydroxy tryptamines and leukotrienes are immediately

released. This leads to clinical features like pruritus, urticaria, angio-oedema, bronchoconstriction and anaphylaxis. Aspirin, opioids, penicillins, radio-opaque iodide containing contrast media and some vaccines commonly causes this type of reaction.

Type II Reaction (cytotoxic reaction)

IgG or an IgM-mediated mechanism plays a role. A Drug acts as hapten. The binding of antibody to cells with subsequent binding of complement leads to cell rupture with immediate release of chemokines. Due to this mechanism haemolytic anemia is caused by drugs like penicillins, cephalosporins, quinine and quinidine. Thrombocytopenia occurs with quinidine, digitoxin, and rifampicin. Drugs like phenylbutazone, chlorpropamide causes neutropenia.

Type III reaction (Immune complex reaction)

They are mediated by intravascular immune complexes. Arises when both drug as antigen and antibodies like IgG or IgM class are present in the circulation and the antigen present in excess. The immune complexes are slowly removed by the phagocytes leading to their deposition in the skin and the microcirculation of joints, kidney, and gastrointestinal system manifested as fever, arthritis, maculopapular rashes and urticaria. Examples of type III reactions are Serum sickness, vasculitis and acute interstitial nephritis. Drugs like penicillin, streptomycin, sulfonamides, NSAIDs causes this type of reaction.

Type IV reaction (Cell-mediated or delayed Hypersensitivity reaction)

Hapten- Protein complex sensitizes T Lymphocytes which causes inflammatory response. Examples include contact dermatitis or delayed skin tests to tuberculin. Contact dermatitis is caused by local anesthetic creams and topical antibiotics. Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN) are Drug related delayed type hypersensitivity reactions which are serious in nature.

Pseudoallergic reaction

Pseudoallergic reactions mimic Type 1 allergic hypersensitivity reaction. Severe reactions are called as anaphylaxis. Such reactions occur after exposure to any drug or radio contrast dye. Certain individuals like asthmatics are more prone to this type of reaction with aspirin.

ADAPTIVE CHANGES

Drug therapy causes adaptive changes which form basis for some adverse reactions. Tardive dyskinesis with long term neuroleptic therapy for schizophrenia is one such adaptive response. Sudden withdrawal of long term drugs leads to rebound reaction as adverse effects. Barbiturate causes restlessness, confusion, convulsions when withdrawn suddenly. Syndrome of acute adrenal insufficiency is seen with withdrawal of long term Corticosteroid therapy.

DELAYED EFFECTS

Carcinogenesis by drugs has been identified due to mechanisms like hormonal, gene toxicity and immune suppression.

Hormonal Mechanism

Increased risk of breast cancer is seen in women taking Hormone replacement therapy for more than 5 years and the risk is 50 %. Carcinoma of uterus risk is increased with tamoxifen treatment for breast carcinoma.

Gene toxicity

This is a Mystery. Examples include:

1) Bladder cancer risk increased with cyclophosphamide which is prevented by using Mesna.
2) Phenacetin abuse leading to carcinomas of renal pelvis
3) Non-lymphocytic leukemia with alkylating agents like melphalan, cyclophosphamide and chlorambucil.

Suppression of immune response

Increased risk of is seen with immunosuppressive drugs like azathioprine after renal transplant. Cancers of liver, biliary tree, soft tissue sarcomas and squamous cell carcinoma are increased in patients taking immunosupressives.

REPRODUCTIVE EFFECTS

A) Fertility impairment

Cytotoxic drugs cause female infertility through ovarian failure. Reversible male fertility impairment due reduced spermatozoa production was caused by sulphasalazine, nitrofurantoin, and Monoamine oxidase inhibitors. Azoospermia leading to permanent impairment was caused by alkylating agents like cyclophosphamide and chlorambucil.

B) Teratogenesis

When a drug is consumed during any trimester of pregnancy developmental anomalies occurs in the fetus. This is called as teratogenesis.

Drugs like phenytoin, carbamazepine and lithium are teratogenic in nature.

C) Drugs in breast milk

Drugs excreted in the breast milk affect fetus.

CLINICAL TRIALS AND DRUG DEVELOPMENT

A drug identified first as lead compound has to undergo preclinical testing in animals and clinical trials in humans which consists of four phases before marketing.

Preclinical toxicity study

The Objectives of Preclinical toxicity studies include: 1) Identifying all potential human toxicities 2) Tests designed to define the mechanisms of toxicities and 3) Predicting the specific and relevant toxicities that is to be monitored in clinical trials.[30] Following are the different types of acute toxicity study methods:

1) Acute toxicity

This study is done to identify single large dose that is lethal in approximately 50% of animals and that is the maximum tolerated dose. Tested with two species, two routes, single dose.[31]

2) Subacute toxicity

This study is done to identify the target organs of toxicity by using three doses, two species which takes 4 weeks to 3months time. If the clinical use is for a longer period then the time taken for the study is also longer. The parameters used are clinical chemistry, physiologic signs, autopsy studies, hematology, histology and electron microscopy studies.[30]

3) Chronic toxicity

Similar to subacute study. Here Rodent and non-rodent species are used for 6 months or more. Sometimes goes hand in hand with clinical trials with controls plus three doses.

The effect on reproductive performance, mating behavior, reproduction, parturition, progeny, birth defects, teratology, perinatal, lactation and post natal changes are studied. It is done simultaneously with clinical trials in drug development.[31]

4) Carcinogenic potential

The study is done for two years in two species so that the drug is used in humans for prolonged periods. Histology, hematology and autopsy results are studied. Rarely transgenic mice for shorter periods as single species is used.

5) Mutagenic potential

The changes on genetic stability, mutations in bacteria (Ames test), and mammalian cells in culture are identified. It determines clastogenicity in mice so as to find the mechanisms of actions of toxicities. Genes and proteins

pathways involved are discovered.It helps to identify safer drugs with new assessment toxicity designs.

Several quantitative estimates like "**no-effect" dose—**the maximum dose at which a specified toxic effect is not seen; the" **minimum lethal dose"—**the smallest dose that is observed to kill any animal; and, the" **median lethal dose" (LD**50**)—**the dose that kills approximately 50% of the animals are studied.[30] LD50 is estimated from a small group of animals.

Limitations of preclinical testing

1. Time-consuming and expensive. The total cost of preclinical studies was estimated around 41 million per successful drug. 2 to 5 years required to collect and analyze data.
2. Animals are needed in large numbers to get valid data. In vitro methods like cell culture and tissue culture are used as alternatives but are having limited value. Animal welfare interested public are opposing animal testing.
3. Toxicity data extrapolation from animals to humans is not reliable completely.
4. Detection of rare adverse effects is not possible.

CLINICAL TRIAL

Clinical trial means a systematic study of a new drug in human subjects to generate data for discovering or verifying the clinical claims or pharmacological and adverse effects with an aim to determine the safety and efficacy of the drug in question.[32] The investigational new drug application has

to be sent to Drug Controller General, Govt. of India, New Delhi before starting trials in humans with all the details of animal studies to get approval. The study started after getting written informed consent from the volunteers.

The clinical trials are conducted in four phases as phase 1, phase 2, phase3 and phase 4.[33]

PHASE 1

Small number of about 25-100 healthy volunteers are used. To study a drug for a disease the concerned patients with particular disease are used. Safety, tolerability, safe clinical dosage range, pharmacokinetic parameters identification and predictable toxicity are assessed.

PHASE 2

About 200 to 400 patients with target disease are used as volunteers. Efficacy, therapeutic benefits and side effects are studied.

PHASE 3

Large scale multicenteric trials in 1000 to 5000 plus patients are conducted to establish safety and efficacy so that errors in phase I and phase 2 trials are minimized. After this New Drug application is filed to Drug Control Authorities.

PHASE 4

This is a post marketing field trial so as to identify rare side effects, unknown interactions, and new uses. 5000 or more number of subjects are used. The manufacturer has to submit Periodic Safety Update Report (PSUR) once in six months in first 2 years and then once in a year for 2 years.

Limitations of clinical trial

Time limit, Size or number of patients, Non Representative patient selection, children and pregnant women exclusion, limited indications, limited concomitant medications usage and more compliant patients in clinical trials are limiting factors.

POST MARKETING SURVEILLANCE

Despite of meticulous monitoring in clinical trial some adverse effects are missed due to the limitations. High incidence ADRs are only identified in clinical trials. Unseen adverse effects occur when a drug is released into the market for use.[34] Hence it became mandatory to do Post marketing surveillance. Post Marketing Surveillance (PMS) is a term used to describe the research and studies associated with product safety evaluation after a drug has been approved for marketing.[35] The activities include collection, reporting and analyzing data. Thus new safety informations are collected.

Methods of Post Marketing Surveillance

The methods include Spontaneous reporting system, Case study, case control studies, Cohort study, Randomized trials, Database research with monitoring and Meta analyses.

Spontaneous reporting system

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other Organization like WHO-regional center, poison control centre that describes one or more adverse drug reactions in a patient who was given one or more

medicinal product that does not derive from a study or any organanized data collection scheme.[36]

The possible relationship between a drug and an adverse event, the relationship being unknown or incompletely documented previously is known as Signal.[37] Signal detection is more important and is needed for signal generation. Many countries have their own pharmacovigilance system.

France

French pharmacovigilance system has a network of 31 regional centers located in teaching hospitals, coordinated with the French Medicines Agency ("Agence Francoise de Securite Sanitaire des Produits de Sante"-AFSSAPS).The databases of French pharmacovigilance system was studied from 1986 to 2001 which showed that report of all drugs and ADRs showing increased reporting overtime by specialist and more for anti-infective drugs.[38]

WHO INTERNATIONAL SYSTEM

The WHO member states are involved in monitoring and reporting. More than 3.7 million cases are reported. WHO programme was established in1968 with centre for drug monitoring in Uppsala in Sweden.

Functions of Uppsala Monitoring Centre

1) New adverse drug reaction identified and analyzed as signals from case report information and submitting to National centres and then to WHO database. At UMC a data mining approach is used.

2) WHO database is used as reference signal for signal strengthening and web based search facilities are available.

3) 'Vigimed' is an e-mail information exchange system which exchanges information between national centres and WHO.

4) Periodical Newsletters, guidelines, books are published.

5) Supply of tools like WHO Drug Dictionary and WHO Adverse Reaction Terminology for management.

6) Training and consultancy support to National centres.

7) "Vigiflow" is the Computer Software for case reporting which is designed to support national centres for case reporting.

8) Conducting annual meeting to discuss scientific and organizational matters.

9) Scientific development of Pharmacovigilance by Methodical research.

US FDA "MedWatch"

MedWatch is the Safety information and adverse event reporting system of US FDA. It gives timely clinical knowledge and safety issues of medicinal products both prescribed as well as over-the-counter drugs, medical and radiation-emitting devices and nutritional products like infant formulas and dietary supplements. Reporting can be done by practitioner on phone, on line, by MedWatch form submission, or by fax. The risk versus benefit is taken into

consideration and if risk is more then FDA can advise for withdrawal of drug from market.

UK 'YELLOW CARD' System

In UK the spontaneous reporting is Yellow Card scheme. Any suspected reaction has to be reported by the Medical and dental profession members and all reports are kept confidential. The following Adverse effects are reported.

1) Halothane induced Jaundice [39]
2) Estrogens and thromboembolism[40]
3) Metochlopropamide and Extra pyramidal side effects
4) Piroxicam induced Congestive cardiac failure
5) Amiodarone induced Hepatitis.

NATIONAL PHARMACOVIGILANCE SYSTEM OF INDIA[41]

National Pharmacovigilance programme was launched in India by the Central Drugs Standard Control Organization, Ministry of Health and Family welfare in November 2004.

The aim is to generate the culture of ADR notification by health care workers like doctors, dentists, pharmacists, nurses. The data is sent in chain like manner from peripheral pharmacovigilance centre to regional centre, from regional centre to zonal centre, from zonal to National Centre and then finally to WHO- UMC.

Limitations of spontaneous reporting system

No direct information, under reporting, inferior quality of information, many influencing factors, and reporters capacity to identify a reaction weakens the spontaneous reporting system.

CASE REPORTS

Previously unidentified adverse effect of drugs come to light by individual case reports. Anorexant drug fenfluramine after using 20 years for weight reduction was found to have associated with valvular heart disease and pulmonary hypertension and was withdrawn.[42]

CASE CONTROL STUDIES

Comparitive analytical retrospective study was conducted so as to identify cases of diseases or events. Controls are selected from general population are used to compare with diseased cases. Useful to find association and also rare adverse events. Smaller size of study population is the major advantage. The disadvantages are difficulty in selecting cases, controls, collecting datas and interpretation of results.

COHORT STUDIES

Cohorts are group of individuals who are identified, characterized and followed over time to determine the outcome incidence. Such studies are conducted both prospectively and also retrospectively. The advantages are predetermined characters, advance information to collect datas, calculation of attributable risk. The disadvantages are biases and cost of study. Rare adverse

event are detected very rarely. The following are some examples: Framingham Heart study, Physicians and Nurses health study.

RANDOMIZED CLINICAL TRIALS

This is a prospective clinical trial which involves two or more groups to assess the effectiveness of drug therapy. Double blinding is done to avoid bias. There are some limitations like controlled situations as per ICH GCP guidelines, duration, cost and sample size. Some ADRs can be identified at this stage.

DATABASE RESEARCH AND MONITORING

The health care records like hospital admissions, out patient's visits, records of pharmacy are made to be recorded and stored in computerized database so that it becomes easy to access and evaluate the association between the exposure and outcome. The advantages are large number of people identified, temporal associations between disease and adverse event, providing datas for pharmaco-epidemiological studies, and cost effectiveness. The disadvantages are accuracy, needs validation and the possibilities of confounding bias.

META ANALYSIS

Results of many individual studies are combined and systematic review is done. Example for Meta analysis was the study conducted to evaluate the association between green tea consumption and the risk of gastric cancer.[43]Some ADRs are analyzed at this level.

ADR AND SYSTEMIC MANIFESTATIONS

Reportable ADR- "All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related."[44] Examples are Hypersensitivity reactions, Life –threatening reactions causing disability, idiosyncratic reactions secondary to drug interactions.

Common drugs causing ADRs

ADRs are commonly caused by Antibiotics, Antineoplastics, Anticoagulants, Cardiovascular drugs, Hypoglycemics, Antihypertensive, NSAID/Analgesics, Diagnostic agents, and CNS drugs. Drugs most involved in ADRs causing admissions are Anti-rheumatics and Analgesics (27%), Cardiovascular drugs(23%), Psychotropic drugs(14%), Antidiabetics (12%), Antibiotics (7%) and Corticosteroids (5%).

ADR AND SYSTEM ORGAN CLASSIFICATION

Dermatologic/Allergic, Hematologic, Central Nervous system, Peripheral Nervous system, Cardiovascular, Respiratory, Gastrointestinal, Renal/genitourinary, Hepatobiliary, Metabolic, Endocrine, Musculoskeletal system are various systems affected by adverse drug reactions. Individual system manifestation is explained as follows.

SKIN AND APPENDAGES DISORDER

Dermatitis - Eczema /exfoliative, Eruptions - fixed, lichenoid, pustular. Urticaria/angioedema, Erythema multiforme, Steven Johnson

syndrome, Toxic epidermal necrolysis, Reactions - photosensitivity, phototoxic, photoallergic reactions are caused by Drugs.

IMMUNOLOGY

Anaphylaxis, drug fever, urticaria, angioedema, serum sickness, malaise, rigors/shivering, withdrawal syndrome/rebound effects are due to adverse drug reactions.

HEMATOLOGIC SYSTEM

Bone Marrow depression / agranulocytosis, hemolysis, cytopenias like anemia, granulocytopenia, nuetropenia, thrombotic thrombocytopenic purpura, vasculitis, coagulation disorders, thrombosis, embolism, thromboembolism - arterial, venous /pulmonary occurs due to drugs.

PSYCHIATRY

Anorexia, apathy, delirium, depersonalization, depression, personality disorder, psychosis, psychotic reaction, thinking abnormalities and thought disturbances are caused by drugs as adverse effects.

CNS/PNS

Sedation - antihistamines, Syncope - chloral hydrate, lithium, neuroleptics, quinidine, Dizziness - antidepressants, calcium channel blockers, nitrates, Enchelopathy, Convulsions - antibiotic ciprofloxacin, Speech disorder, Dysphonia, Hypertonia, Hypotonia, Paralysis,

Neuropathy - Nitrofurantoin, gait abnormality, extra pyramidal disorder, choreoathetosis, dyskinesia - metachlopramide, oculogyric crisis,

anticholinergic syndrome, neuroleptic malignant syndrome and serotonin syndrome.

EYE

Cataract, keratitis, retinal disorder and vision abnormalities.

ENT

Ototoxicity

CARDIOVASCULAR SYSTEM

Cardiac failure including shock - beta blockers, circulatory failure, hypertension-systemic and pulmonary, hypotension including postural - hydralazine, syncope, Mycarditis, cardiomyopathy, angina pectoris, infarction, ischemia, coronary artery disorder, thrombosis, endocarditis, mitral insufficiency, fibrosis - endocardial, pericarditis, hemopericardium, pericardial effusion, Arrhythmias, AV block, cardiac arrest, fibrillation - atrial/ventricular, palpitation and torsa de pointes are caused by drugs as adverse reactions.

RESPIRATORY SYSTEM

Adult respiratory distress syndrome, asphyxia, hypoventilation/ hypercapnia, hypoxia, dyspnoea, apnoea, bradypnoea, asthma / COPD-beta blockers, Pneumonitis /alveolitis-Nitrofurantoin, interstitial lung disease, pulmonary fibrosis, pulmonary edema and respiratory depression/ arrest are caused as adverse reactions to drugs.

GIT

Inflammation of esophagus, gastroduodenal region - antibiotics, colon - antibiotics, ascites, diarrhea, constipation, dyspepsia - OHAS, upper

gastrointestinal bleeding - corticosteroids, pancreatitis-antibiotics, abdominal pain, dyspepsia, git infarction/necrosis/gangrene, hematemesis/melena/ hematochezia, paralytic ileus, intestinal ischemia, obstruction, perforation, stenosis, and peritonitis are adverse reactions to drugs.

HEPATOBILIARY SYSTEM

Cholestatic jaundice, hepatocellular jaundice, mixed, LFT abnormalities, Hepatitis - Nitrofurantoin, antidepressants, viral hepatitis like - halothane, isoniazid, phenytoin, focal hepatitis - aspirin, chronic hepatitis-methyldopa, diclofenac, zonal necrosis-paracetamol and carbon tetrachloride, cholestasis - oral contraceptives, anabolic steroids and androgens, inflammatory cholestasis - allopurinol, co-amoxiclav, carbamazepine, ductal cholestasis - chlorpromazine, flucloxacilln, microvesicular steatosis - aspirin, ketoprofen and tetracyclines, Macro vesicular changes - acetaminophen, methotrexate, phospholipidosis, Granulomas - allopurinol, phenytoin, isoniazid, quinine, penicillin, quinidine, venocclusive disease-chemotherapeutic agents, bush tea, peliosis hepatis - anabolic steroids, hepatic vein thrombosis - oral contraceptives, Neoplasm - vinyl chloride combined oral contraceptives, anabolic steroids arsenic and thorotrast are various adverse effects.

GENITOURINARY SYSTEM

1) Urinary retention-trihexylphenidyl 2) Hematuria - warfarin 3) Acute kidney injury - ACE I, ARB, NSAID, immunosuppressants 4) Tubular epithelial damage - ATN-AGs, contrast agents, platins, fovirs, immunosuppressants 5) Osmotic nephrosis - mannitol, ig, dextran

6) Tubulointerstistial disease like allergic interstitial nephritis-penicillin, ciprofloxacin, NSAIDs, PPI, loop diuretics, 7) Nephrocalcinosis - sodium phosphate, 8)Papillary necrosis - analgesics, 9) Glomerular nephritis - gold, lithium, NSAIDs, vasculitis 10)Thrombosis - hydralazine, propyl thiouracil, chelators, allopurinol, pencillamine 11) Obstructive nephropathy (intratubular) - acyclovir, sulfa drugs, indinavir,12) Nephrolithiais - sulfa drugs, triamterene and thrombolytics.

ENDOCRINE SYSTEM

Amenorrhea, loss of libido, hypoglycemia, hyperglycemia, weight loss and weight gain are adverse effects caused by drugs.

METABOLIC AND NUTRITONAL DISORDERS

Fluid and electrolyte disturbances, retention - corticosteroids, dehydration - diuretics, hypoglycemia - insulin, oral hypoglycemic agents, acidosis and gout are adverse effects of drugs.

MUSCULOSKELETAL AND COLLAGEN VASCULAR DISORDERS

Rhabdomyolysis - atorvastatin and fluconazole, pathological fracture, myopathy, myositis, osteoporosis, LE syndrome, retroperitoneal fibrosis and vasculitis are adverse effects caused by drugs.

Since the study is related with drug induced skin reactions the detailed description of these reactions follows.

Drug induced skin reaction

Cutaneous drug reactions are caused by several different mechanisms like immunological or non-immunological and this was already explained in

the mechanism of ADR. The drugs most often responsible for eruptions are antimicrobial agents and antipyretic/anti-inflammatory analgesics.[45]

Diagnosis

The drug reactions cannot be easily distinguished from naturally occurring eruptions. Uncertainty prevails. Drug rash may be similar to rash in viral infection.

When more than one drug is taken then the reaction to one particular drug is difficult to establish. Severe reactions affects mucous membrane, causes blisters, skin detachment, fever, edema lips and genitals, face, necrosis of skin, and breathing difficulties.

The useful diagnostic tool is timing of reaction. Reaction occurs within a few weeks of drug intake with few exemptions. Knowledge about half life of drug is important so that withdrawal is done accordingly. The risk–benefit potential is considered before discontinuing drugs.

Treatment

1) Symptomatic treatment 2) Calamine lotion or systemic antihistamines to relieve pruritus 3) topical corticosteroids for local inflammation. 4) Systemic corticosteroids-for extensive skin lesions.

CLASSIFICATION OF DRUG INDUCED CUTANEOUS ERUPTIONS

MACULOPAPULAR RASH / DRUG RASH

Maculopapular rash is the most common type of drug induced skin reaction. They manifests as exanthematous lesion like macules which are small, distinct, flat areas and papules which are small, raised lesions. The red itchy

lesion appears over trunk, extremities and intertriginous areas. Palm and sole also affected.

Immunohistochemical the mononuclear cellular infiltrate consists mainly of CD3+T cells and CD4+T cells in dermis, both CD4 and CD8 cells in dermoepidermal junction zone adjacent to basal keratinocyte.[46] The drugs that causes this type of reaction are penicillins, sulfonamides, cephalosporins, chloramphenicol, gentamicin, erythromycin, amphotericin, antituberculous drugs, nalidixic acid, nitrofurantoin, allopurinol, barbiturates, phenytoin thiazides, furosemide, captopril, carbamazepine, gold salts, lithium, phenothiazines, phenylbutazone ,quinidine and thiouracil.

Fixed drug eruption

Manifests as erythematous round or oval lesions of a reddish, purple or brown colour, with vesicles or bullae. Single lesion appears first. Affects skin and mucosa. Frequently affected sites are feet, hand, tongue, external genitalia and perianal region. Eruption occurs at the same site along with new lesions whenever the causative drug is taken.[47] Heals within 7-10 days after stopping the drug. Pathogenesis is poorly defined. Genetic susceptibility is seen.[48]

There are many causes like food additives, drugs and pharmaceutical excipients. Tetracycline and Co-trimoxazole commonly causes lesions on glans penis.[49] Oral challenge to confirm the diagnosis is accepted and practised safely. Topical corticosteroid reduces the reaction intensity.

Common drugs causing fixed drug eruptions are ACE inhibitors, allopurinol; Antimicrobials- penicillin, sulfonamides, tetracyclines,

cephalosporins, co-trimaxazole, metronidazole, fluconazole; Calcium channel blockers- amlodipine, diltiazem; Barbiturates, Benzodiazepines, Dextromethorphan, Carbamazepine, Lamotrigine, NSAIDs, Paclitaxel, Paracetamol, Phenolphthalein; Proton pump inhibitors- omeprazole, lansoprazole; and Mercurial diuretics.

Erythroderma / Exfoliative dermatitis

Erythematous rash with desquamation occurs as a severe reaction pattern due to drug. Systemic symptoms like fever, lymphadenopathy and anorexia are also present. Associated complications are hypothermia, fluid and electrolyte loss, and infection. Drugs causing such reactions are penicillin, sulfonamides, chloroquine, isoniazid and phenytoin.

Urticaria and Angio-oedema

Second most common form of cutaneous drug reaction after maculopapular rash. Also known as nettle rash or hives. Urticaria is associated with anaphylaxis, angio-oedema or serum sickness. Often becomes more severe leading to death. Present as raised, itchy, red blotches or wheals with pale centre. Rapid onset in nature occurs within hours of exposure.

Utricarial swelling of deep dermal and subcutaneous tissues, mucous membranes is called as Angioedema which is a vascular leakage. When angioedema affects respiratory tract obstruction, it leads to death.

Serum sickness has systemic symptoms like fever and arthralgia. Lips, tongue and genitals are affected. Mechanisms involved are immunologic

histamine release and non-immunologic histamine release. Ig E, Complement activation, release of cutaneous mast cell mediators, and altered chemical pathways such as arachidonic acid metabolism plays role in the mechanism. Serum sickness like reaction differs from true serum sickness by absence of immune complexes, hypocomplementaemia, vasculitis and renal involvement.[50] .

Skin tests like radio allergen absorbent test (RAST), leukocyte, histamine release, tryptase measurement help to identify the cause. Positive rechallenge confirm the cause.

Drugs causing urticaria / angioedema with specific mechanism is explained as follows:

1) Drugs acting through IgE receptors: A) Antibiotics-penicillins, cephalosporins, sulfonamides, tetracyclines B) Antiepileptics
2) Drugs that cause mast cell degranulation: Opioids, codeine, tubocurarine, atropine, quinine, hydralazine, vancomycin, radio contrast media and pentamidine.
3) Drugs that pharmacologically promote or exacerbate urticaria monoclonal antibodies: Aspirin, NSAIDs and ACE inhibitors.
4) Immune complex formation: Thiouracils, penicillin, sulfonamides.
5) Precipitation and activation of complement: Cholecystographic dyes and amino salicylic acid.

6) Excipients in the medication like Benzoic acid, butylated hydroxytoluene, sulfites, aspartame, colourings, and preservatives provoke allergic or pseudoallergic reactions.

Acneiform eruptions

The drug eruptions resemble acne vulgaris. Papulopustular lesions appear without comedones. Drugs causing such reactions are oral contraceptives, haloperidol, corticotrophin (ACTH), androgens (in females), corticosteroids, isoniazid, phenytoin, iodides and lithium.

Psoriasiform eruptions

Eruptions are similar to idiopathic psoriasis and consist of erythematous plaques covered by large dry silvery scales. Reaction time is less than one month to 3 month. Drugs that cause psoriasiform eruptions or exacerbate psoriasis are as follows: Alfa interferons, beta blockers, lithium, ACE inhibitors, NSAIDs, chloroquine, hydroxychloroquine, terbinafine, digoxin, penicillamine, gold, granulocyte colony-stimulating factor (G-CSF), tumor necrosis factor and tetracycline.

Purpura

The lesion is small cutaneous extravasations of blood. It is an occasional drug-induced skin eruption. Platelet function tests are within normal limits. Common drugs causing this type of reaction are aspirin, sulfonamides, quinine, penicillin and atropine.

Vasculitis

Inflammation of the blood vessel is called as vasculitis. Vasculitides is a diverse group of conditions presents as systemic or cutaneous disorder. The mechanism is due to Type III hypersensitivity reaction with immune complex deposition in capillaries. Raised purpuric (purple) lesions size of about a pin head to few centimeters is seen over leg. Sometimes hemorrhagic blisters and ulceration also seen over upper extremities and trunk .

1) Leukocytoclastic vasculitis is the most common type. For accurate diagnosis skin biopsy is needed in which the histopathological features of necrosis of cutaneous blood vessel walls with neutrophil infiltration are seen.
2) Another type of vasculitis is Henoch–Schonlein purpura which involves other systems like joints, gastrointestinal system, heart, central nervous system and kidneys. Aspirin, penicillins, quinidine, gold are associated with this type of vasculitis.
3) Rare types of vasculitis are polyarteritis nodosa-like vasculitis, pustular pigmented purpuric dermatoses and pustular hypersensitivity vasculitis.

The following drugs causes cutaneous vasculitis: Beta-lactam antibiotics, Cotrimoxazole, Minocycline, Erythromycin, sulfonamides, Allopurinol, Hydralazine, Carbamazepine, NSAIDs, Interferon's, Granulocyte-Macrophage colony stimulating factors, Penicillamine, Diltiazem, Propylthiouracil, Retinoids, Gold, Sulfasalzine, Furosemide and Thiazides.

Erythema Multiforme, Stevens–Johnson syndrome and Toxic Epidermal Necrolysis

Erythema Multiforme (EM), Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe drug induced cutaneous reactions. Fever and a flu-like syndrome develop before skin eruption.

Erythema, blisters, papular lesions affects trunk, hands, feet and limbs. Target or iris lesion is the characteristic feature of Erythema Multiforme. Mucosa of mouth, eyes and genitalia are affected in Steven Johnson syndrome. (SJS) Fever, malaise, arthralgia, myalgia with extensive erythema multiforme of face and trunk is seen in SJS. Fatality rate is 5%.

The reaction mainly involves CD4+ T cells and CD8+ T cells. CD4+ T cells predominant in upper dermis while epidermal CD8+ T cells and macrophages are variable and Langerhans's cells virtually disappear.[51] Inducible Nitric acid synthase is demonstrable in skin in SJS/TEN indicating the role of nitric oxide in keratinocyte apoptosis and necrosis.[52]

Erythema Multiforme or Stevens–Johnson Syndrome are caused by drugs like co-trimoxazole, sulfonamides, macrolides, penicillins, cephalosporins, barbiturates carbamazepine, phenytoin, lamotrigine, NSAIDs, gold, rifampicin,histamine, H2-antagonist, leflunomide, thiazides and chlorpropamide.

Toxic Epidermal Necrolysis

Lyell's syndrome or toxic epidermal necrolysis is characterized by widespread full-thickness epidermal necrosis involving 30% and more areas of

body surface. The mortality is high around 40%. Co morbid conditions like HIV infection, systemic lupus erythematosus and bone marrow transplant recipients worsen this condition. Lesion starts on face or upper trunk as erythematous macules, irregular target-like bulla or erythema. Massive epidermal loss causes dehydration, increased energy expenditure, septicemia due infection, organ dysfunction and finally death. The reaction starts with in 2-8 weeks of drug intake and may progress inspite of discontinuation.

The drugs causing toxic epidermal necrolysis are antitubercular drugs, NSAIDs, carbamazepine, sulfonamides, penicillins, griseofulvin, tetracyclines, gold, leflunomides, allopurinol and barbiturates.

Blistering drug eruption

Flaccid blisters along with erythema, scaling are seen in pemphigus. Linear IgA deposition along the basement membrane zone is seen. Drug induced reaction is manifested as phemphigus like lesion and also similar to porphyria cutanea tarda, pemphigoid and linear IgA bullous dermatosis. Drugs and types of reaction follow:

1) Pemphigus: gold/sodium aurothiomalate, captopril, cephalosporins, penicillin, piroxicam and penicillamine.

2) Bullous pemphigoid: penicillamine, chloroquine, furosemide, ACE inhibitors, sulphasalazine and penicillin.

3) IgA bullous dermatosis: lithium, ceftriaxone, co-trimoxazole, furosemide, G-CSF, interleukin-2, captopril, NSAIDs, penicillin, rifampicin and vancomycin.

4) Pseudoporphyria cutanea tarda: tetracycline, NSAIDs, furosemide and thiazides.

Photosensitivity:

The reaction occurs to photosensitizing agent which may be topical or systemic drug. The reaction may be photo-toxic or photo-allergic and occurs within 5-20 hrs of exposure as erythema, blisters and desquamation. This reaction forms 8% of cutaneous drug reactions. The drugs associated are demeclocycline, sulfonamides, lomefloxacin, amiodarone, antidepressants (tricylic, MAOIs), phenothiazines, carbamazepine, quinine, quinidine, retinoids, St John's Wort, sulphonylureas and thiazides.

Lichenoid drug eruptions

The reaction resembles idiopathic lichen planus. Arsenicals used in the treatment of syphilis are the first drug that has caused lichenoid reaction. Small purplish polygonal papules are seen over trunk and legs. CD4+Tcells capable of producing IFN gamma and TNF alpha have been implicated in the development of lichenoid drug eruption.[53] Drugs that cause this reaction are antimalarials, arsenicals, captopril, methyldopa, penicillamine, carbamazepine, furosemide, phenytoin, gold, sulfonylureas, proton pump inhibitors and beta blockers.

Pigmentary disorders

Skin colour changes are seen due to drug intake. Localised or widespread Pigmentation is seen. Like chloasma, affects the arms, face, neck, shins and pretibial areas. Melanin pigmentation is altered. Corneal depositions and retinal damage also frequently coexists in some patients. Rarely reaction may persist for years.

The drugs causing pigmentation are Mepacrine (yellow), Amiodarone (slate grey), Chloroquine (blue-grey or brown), Gold (blue-grey), Chlorpromazine (blue-grey), Gold (blue-grey), Phenytoin (brown), Minocycline, Cytotoxic agents and Oral contraceptives(brown), rifampicin (red) and Methylsergide maleate (red).

Alopecia

Alopecia is hair loss caused by many drugs. Daily 100 hairs are shed out of 100000 hairs. Three cyclical stages namely anagen, catagen, telogen are undergone by hair follicles which lasts for 3 years. Anagen is growing phase. Catagen is involutionary phase. Telogen is the resting phase.

Soft and colourless hairs over palms and soles are called vellus hairs. Over scalp, eyebrows, axillae are large pigmented, coarse hairs called terminal hairs. Anagen effluvium is drug induced cessation of anagen growth. Telogen effluvium is drug induced hair loss in telogen phase. Hair loss is seen over scalp, eyebrows and pubic area.

Androgenic alopecia is male pattern baldness seen in women due to drugs with androgenic activity like metyrapone, anabolic steroids, danazol and estrogen receptor antagonist tamoxifen.

Drugs causing alopecia are as cyclophosphamide, bleomycin, platinum compounds, vinca alkaloids, amphetamines, heparin, warfarin, heparinoids, leflunomide, interferons, oral contraceptives, lithium, cimeditine, antithroid drugs and cimetidine.

Excess hair growth

Excessive growth of coarse hair with masculine features is called as Hirsutism. Occurs due to androgenic stimulation of hair follicles by hormones. Drugs commonly responsible include testosterone, danazol, corticotrophin, anabolic steroids and glucocorticoids.

The growth of terminal or vellus hair is called as hypertrichosis. Hypertrichosis caused by minoxidil is used for male pattern baldness as topical application. Hypertrichosis is caused by drugs like nifedipine, penicillamine, cyclosporine, phenytoin, diazoxide, methoxalen and verapamil.

Nail disorders

Nail changes like horizontal notches (Beau's line), brittle nails, separation of nail plates (onycholysis) and erythema over nail folds (paronychia) are caused by drugs. May be due to toxic effect of drug on the epithelia of nail and blood vessels of nail bed leading to necrosis.

The drugs causing nail disorders are lithium, chloramphenicol, chlorpromazine, pencillamine, gold, thiazides, retinoids, captopril, cytotoxic agents, fluroquinolones and tetracyclines.

Measures to prevent ADR:

Adverse effects also occur due to human errors. The physician should ask history of prior allergies and adverse reactions in all patients before prescribing drugs. Other history like concomitant medication, OTC, substance abuse alternative forms of medications should be enquired. Clarity must be there while writing the drug, route, frequency and duration in the case records. Short hand forms and abbreviations are not to be used by physicians. After giving instructions to the patient feedback should be obtained. No drugs should be given over phone.

Adverse drug reactions are preventable in most of the cases if provoking factors are identified as early as possible. Early intervention is must to avoid mortality.

This study is designed to bring about the findings which may help to minimize the impact due to ADRs.

AIM AND OBJECTIVES OF THE STUDY

To study the profile of different clinical manifestations of drug induced skin reactions in the patients attending outpatient department of Dermatology in a tertiary care hospital.

Primary objective

- To analyze different groups of drugs causing drug induced skin reactions.

Secondary objective

1. To describe the Causality analysis of drug induced skin reactions by using WHO causality assessment scale[54] and Naranjo's algorithm.[55]
2. To describe the severity analysis of drug induced skin reactions by using Hartwig and Seigel scale.[56]
3. To describe the nature of different types of skin reactions.
4. To describe socio-demographic profile in drug induced skin reactions.
5. To investigate the role of gender in causing drug induced skin reactions.
6. To analyze the predisposing factors.

MATERIALS AND METHODS

Study Design: Descriptive study.

Study Period: September 2011 to February 2013

Study centre: Dermatology Out-patient Department, Government Kilpauk Medical College, Chennai-10.

Study population: Patients with drug induced skin reactions attending Out-patient Department of Dermatology.

Sample Size: All patients with drug induced skin reactions who attend the OPD of dermatology

Inclusion criteria

1. Patients of all ages, belonging to both genders presenting to Dermatology Out-patient clinic with skin reactions following intake of any drug.
2. Patients referred from other clinical specialties to Dermatology OPD for the treatment of drug induced reactions.

Exclusion Criteria

1. Patients with other skin conditions.
2. Patients not willing to consent for participation in the study.

Ethical consideration

The study was approved by the Institutional Ethics Committee.

Confidentiality and anonymity of the patients information were maintained during and after the study.

Treatment and care of the patient was not interfered during the study process.

Study Procedure

All the patients with drug induced skin reaction attending the Dermatology outpatient department were registered after obtaining informed consent. Patients with other skin reactions were excluded. All the details regarding patient's basic data, present illness, past medical history, co-morbidities, concomitant medications, and family history were collected and recorded in the proforma. Details of the drugs suspected to be causing ADR and the details of cutaneous lesions were recorded in the proforma. A detailed clinical history and physical examination was done. The prescription details available with the patient were also collected. The clinical diagnosis of drug induced skin reaction was confirmed by the dermatologist.

The data was recorded in the Suspected Adverse Drug Reaction Reporting Form obtained from Central Standard Control Organisation.[57] The patient's initials but not the names were recorded to maintain the privacy and confidentiality. Basic data like age, gender, height, weight were recorded. .Details of cutaneous reaction like date of start and recovery, type of cutaneous ADR. were recorded. Details of suspected drug causing ADR, and details of concomitant medications were recorded. The relevant medical history and details of applicable test in relation to cutaneous reaction were recorded. The data were analyzed and causality assessment of ADR was done by using WHO

causality assessment scale[58] and Naranjo Algorithm.[55] Severity of ADR was assessed by Modified Hartwig and Siegel Assessment Scale.[56]

Statistical Analysis

Data collected were categorically charted on a Windows Microsoft 2007 system. The data was analyzed using SPSS software, Stat graphics plus and Excel. Diagrams and graphs were used to make relevant comparisons. Statistical significance was analyzed by using Chi- Square Test.

RESULTS

The details of 100 cases were recorded. All details recorded as per "CDSCO suspected adverse drug reporting forms" were analyzed. The data was analyzed using suitable statistical packages. Various statistical significant tests were used to find the parametric significance and inferences were derived. The details are described below.

Patients' demographic details like age and gender analysis were done.

AGE:

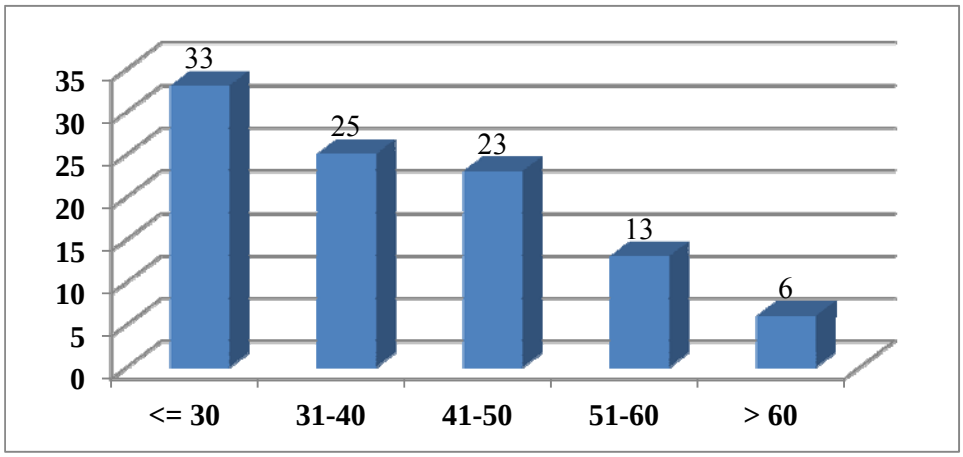
The age wise distribution of ADRs in different age groups is shown below:

Table 1: Age wise distribution

Age in years	Frequency	Percent
<= 30	33	33.0
31-40	25	25.0
41-50	23	23.0
51-60	13	13.0
> 60	6	6.0
Total	100	100.0

33% of drug induced skin reaction was common in the age group years ≤30 years. 6% of ADR was seen above 60 years.

Figure 1: Age wise distribution



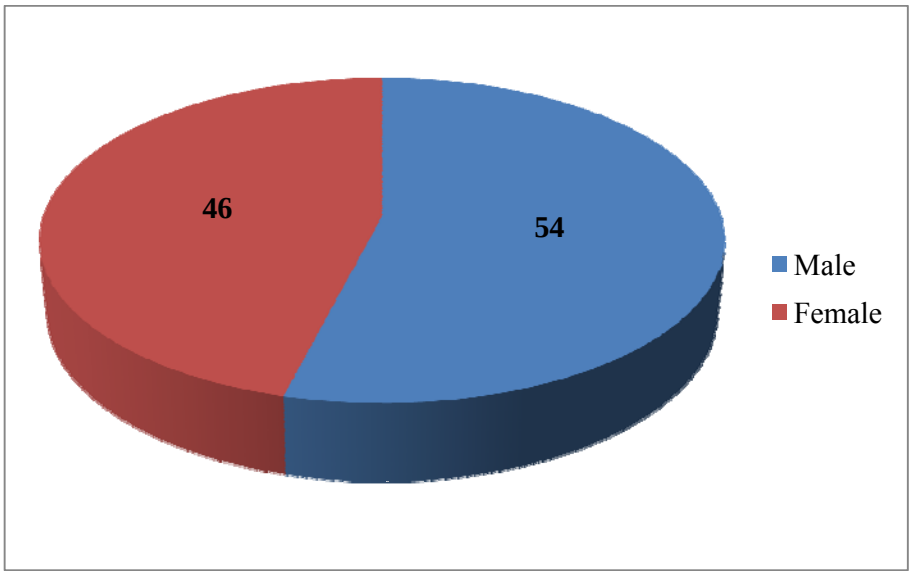
GENDER:

Table 2: Gender distribution of patients with ADRs

Gender	Frequency	Percent
Male	54	54.0
Female	46	46.0
Total	100	100.0

.
Drug induced skin reaction was found more in males compared to females.

Figure 2: Gender distribution of patients with ADRs



ONSET OF DRUG REACTION

Table 3: Time interval between drug intake and onset of drug reaction

Time of onset	Number of cases
1st day	13
2nd day	23
3rd day	18
4th day	7
5th day	8
6-14th day	16
15th -21st day	5
22nd -28th day	2
28th -35th day	3
36th -42nd day	3
43rd -49th day	1
50th -56th day	1

On the day of drug intake 13 cases were affected by drug induced skin reaction. More number of cases was seen after 24 hours.

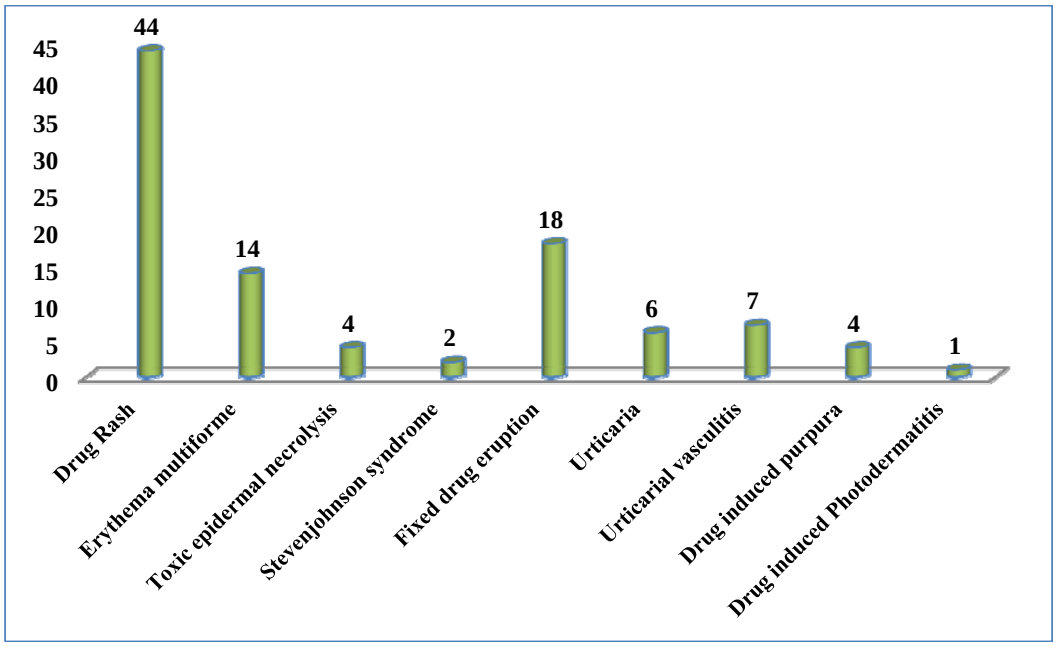
ADVERSE REACTION – PROFILE OF DRUG INDUCED SKIN REACTION

Table 4: Frequency of different types of Drug induced skin reactions

Drug reaction	Frequency	Percent
Drug Rash	44	44.0
Erythema multiforme	14	14.0
Toxic epidermal necrolysis	4	4.0
Steven-Johnson syndrome	2	2.0
Fixed drug eruption	18	18.0
Urticaria	6	6.0
Urticarial vasculitis	7	7.0
Drug induced purpura	4	4.0
Drug induced Photo dermatitis	1	1.0
Total	100	100.0

Most common drug induced skin reactions was Drug Rash (44%).

Figure 3: Frequency of different types of Drug induced- skin reaction

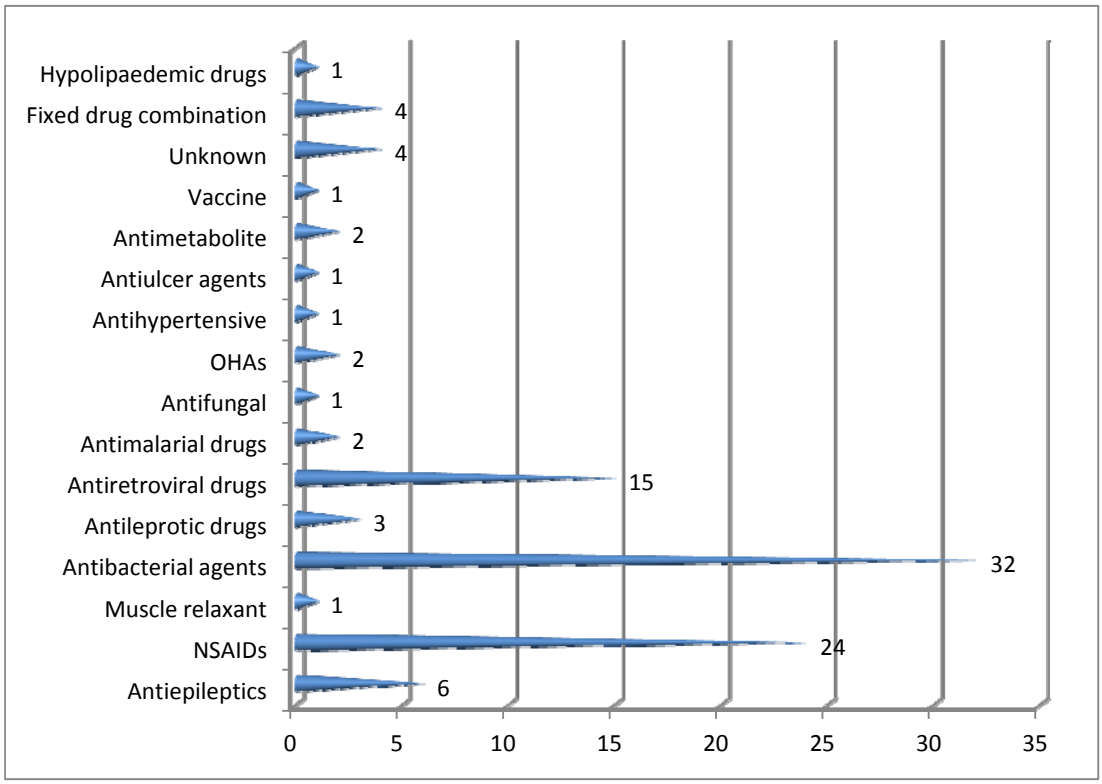


SUSPECTED DRUGS

Table 5: Frequency of various groups of drugs suspected to be the causative agents

Suspected drugs	Frequency	Percent
Antiepileptics	6	6.0
NSAIDs	24	24.0
Muscle relaxant	1	1.0
Antibacterial agents	32	32.0
Antileprotic drugs	3	3.0
Antiretroviral drugs	15	15.0
Antimalarial drugs	2	2.0
Antifungal	1	1.0
OHAs	2	2.0
Antihypertensive	1	1.0
Antiulcer agents	1	1.0
Antimetabolite	2	2.0
Vaccine	1	1.0
Unknown	4	4.0
Fixed drug combination	4	4.0
Hypolipaedemic drugs	1	1.0
Total	100	100.0

Figure 4: Frequency of various groups of drugs suspected to be the causative agent



Antibacterial agents are most commonly causing drug induced skin reaction followed by NSAIDs.

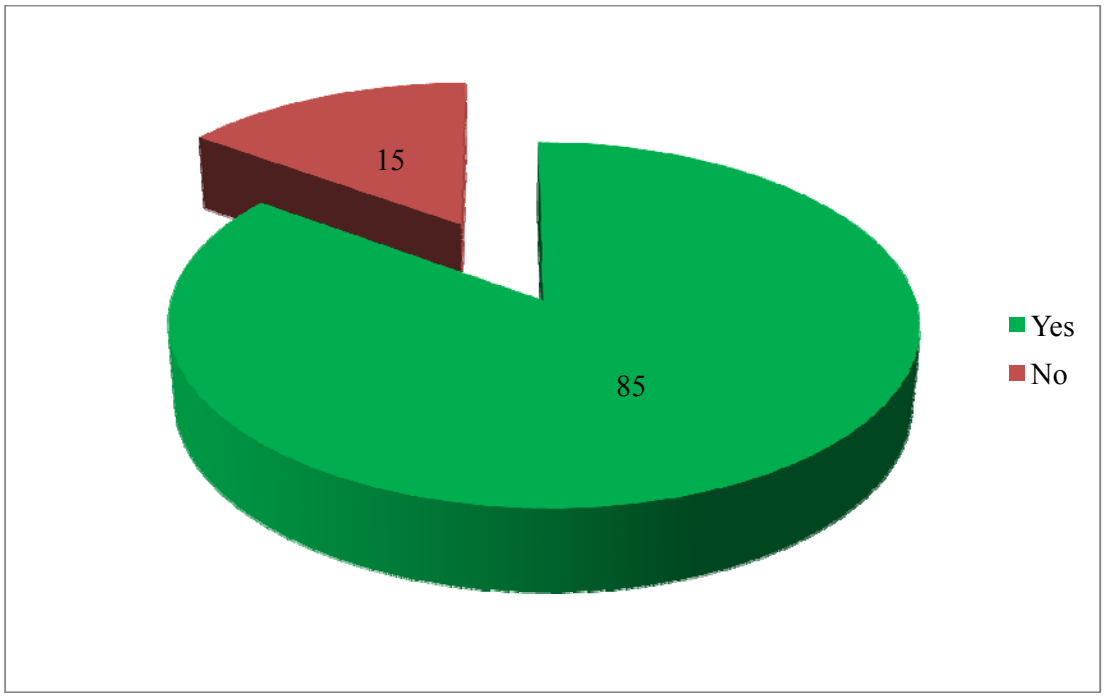
CONCOMITANT MEDICATIONS

Table 6: Pattern of use of Concomitant Medications

Concomitant medications	Frequency	Percent
Yes	85	85.0
No	15	15.0
Total	100	100.0

Concomitant medications were used in 85% of Cases.

Figure 5: Pattern of use of Concomitant Medications



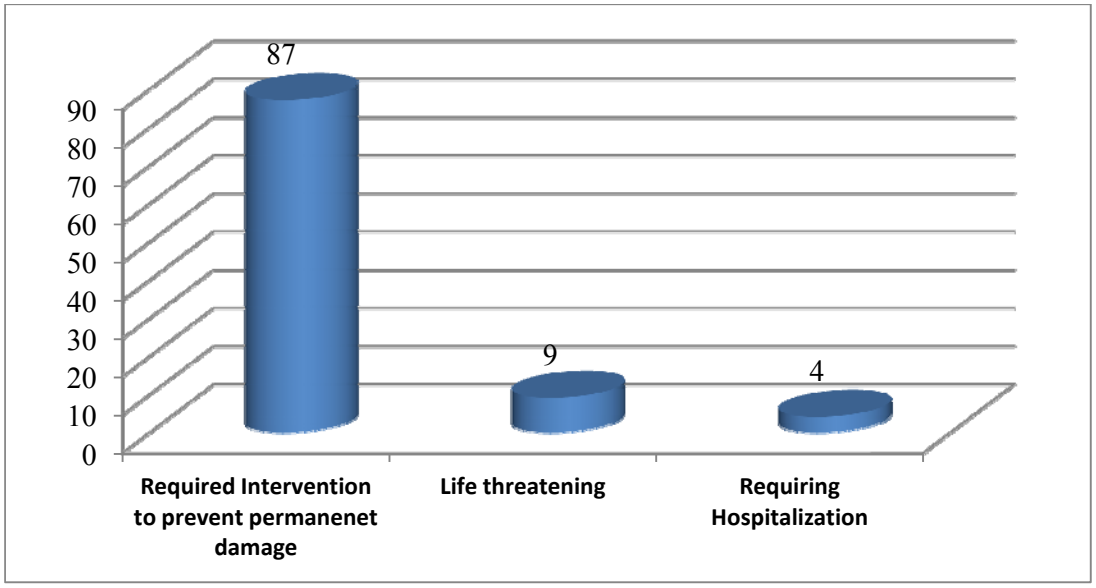
SERIOUSNESS OF REACTION

Table 7: Distribution of Seriousness of reaction

Seriousness of reaction	Frequency	Percent
1) Required Intervention to prevent permanent damage	87	87.0
2)Life threatening	9	9.0
3) Requiring Hospitalization	4	4.0
Total	100	100.0

87 % of cases required intervention to prevent permanent damage, and 9% of cases were life threatening required intensive monitoring.

Figure 6: Distribution of Seriousness of reaction



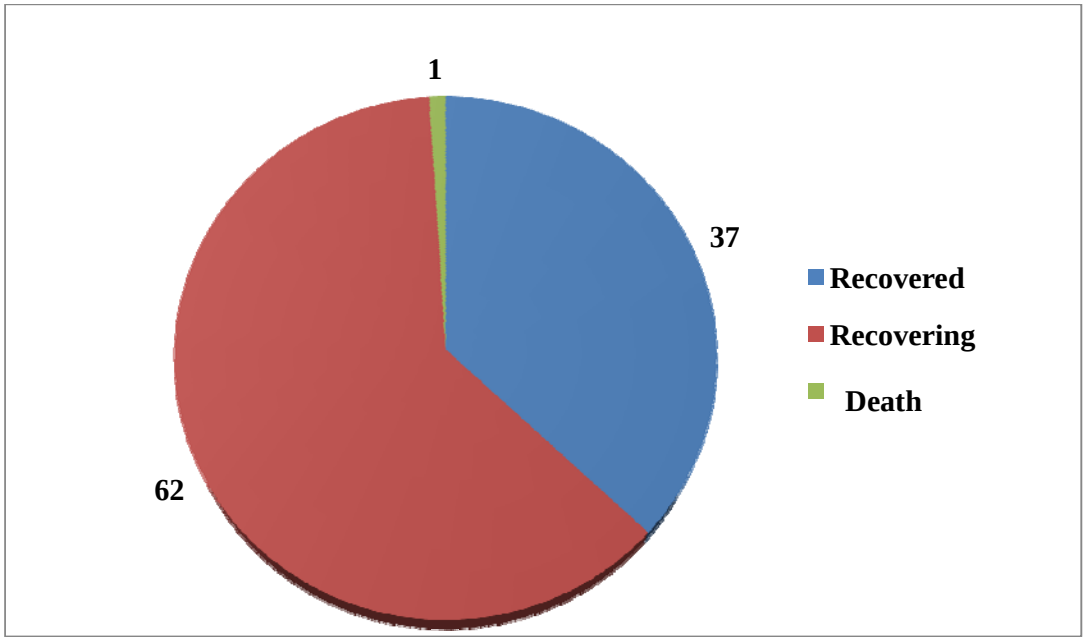
OUTCOME

Table 8: Distribution of outcome

Outcome	Frequency	Percent
Recovered	37	37.0
Recovering	62	62.0
Death	1	1.0
Total	100	100.0

One case died, 37 cases recovered and 62 cases were in recovery phase regarding outcome.

Figure 7: Distribution of outcome



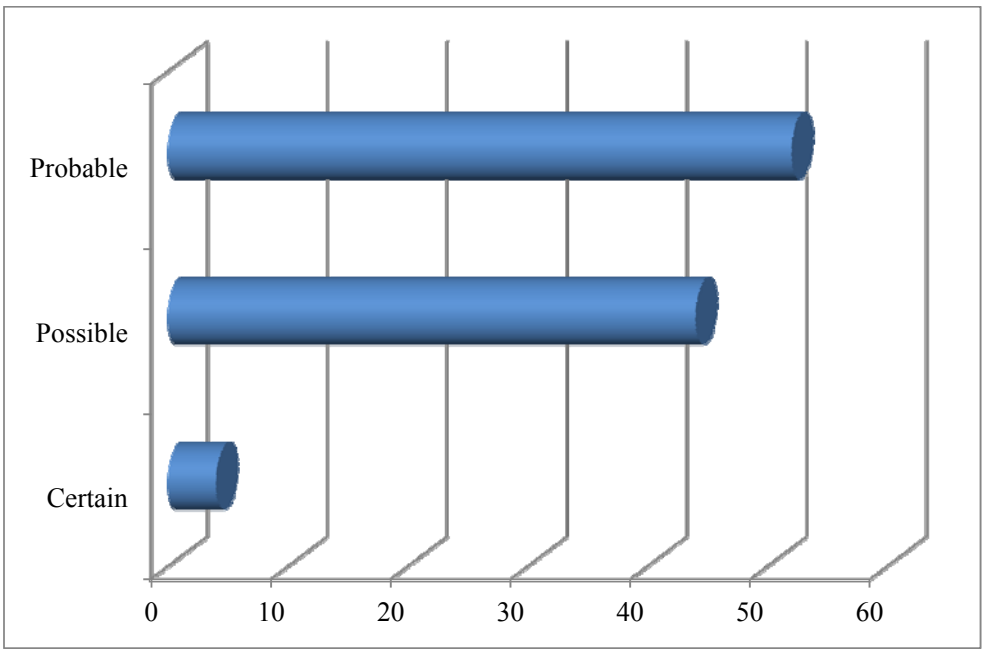
CAUSALITY ASSESSMENT OF ADR

Table 9: Causality Assessment of ADRs by WHO Scale

Causality assessment	Frequency	Percent
Certain	4	4.0
Possible	44	44.0
Probable	52	52.0
Total	100	100.0

Maximum ADRs were Probable (52%). 44 ADRs were Possible and only 4 ADRs were Certain.

Figure 8: Causality Assessment of ADRs by WHO Scale



CAUSALITY ASSESSMENT OF ADR:

Table 10: Causality assessment ADRs by Naranjo Algorithm

Causality assessment	Frequency
Possible	0
Probable	100
Definite	0

By Using Naranjo Algorithm all ADRs were Probable with score of 6-7.

ADR SEVERITY ASSESSMENT SCALE:

Table 11: ADR severity assessment by using Modified Hartwig and Siegel Scale-1992

	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7
Number of ADRs	0	0	87	4	8	0	1

87 % of ADRs were moderately severe requiring discontinuation of the suspected drug and was amenable to management with medications as outpatient.

Age versus seriousness of reaction

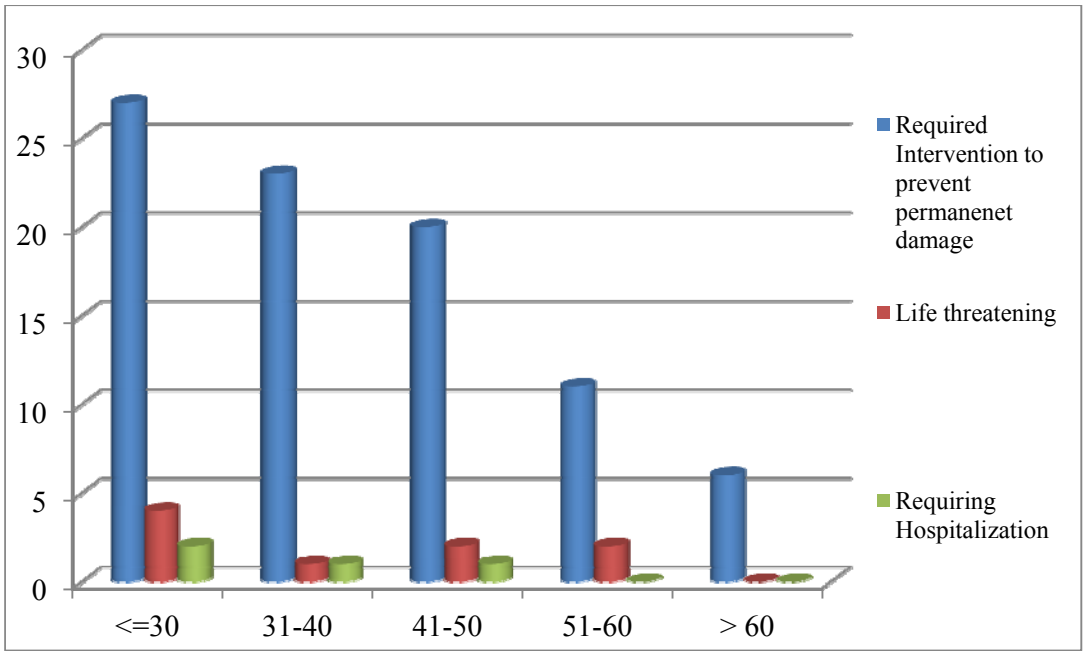
Table 12: Distribution of Age versus seriousness of reaction

		Seriousness of Reaction			Total
Age in years		Required Intervention to prevent permanent damage	Life threatening	Requiring Hospitalization	
1.	<= 30	27	4	2	33
2.	31-40	23	1	1	25
3.	41-50	20	2	1	23
4.	51-60	11	2	0	13
5.	> 60	6	0	0	6
Total		87	9	4	100

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.599(a)	8	.891
Likelihood Ratio	4.890	8	.769
Linear-by-Linear Association	.994	1	.319
N of Valid Cases	100		

Figure 9: Distribution of Age versus seriousness of reaction



All ADRs required intervention in all age groups.

AGE VERSUS OUTCOME OF ADRs:

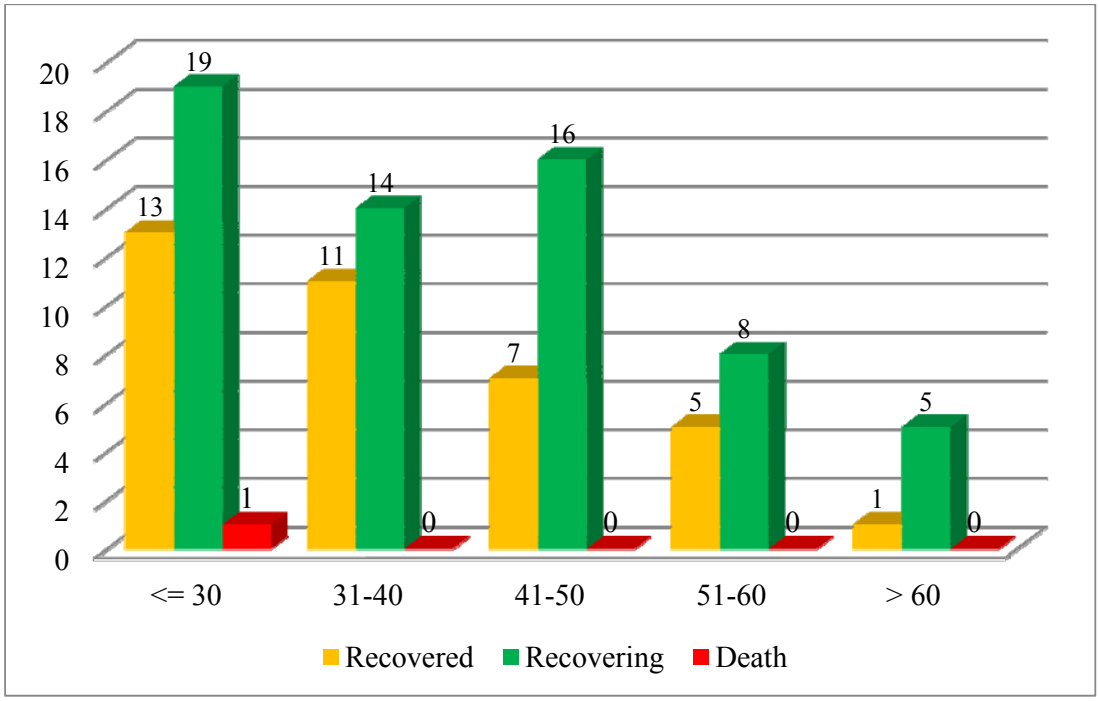
Table 13: Distribution of outcome of ADRs in different Age Groups

			Outcome			Total
			Recovered	Recovering	Death	
Age Group in years	<= 30	Count	13	19	1	33
		% within Age Group in years	39.4%	57.6%	3.0%	100.0%
		% within Outcome	35.1%	30.6%	100.0%	33.0%
	31-40	Count	11	14	0	25
		% within Age Group in years	44.0%	56.0%	.0%	100.0%
		% within Outcome	29.7%	22.6%	.0%	25.0%
	41-50	Count	7	16	0	23
		% within Age Group in years	30.4%	69.6%	.0%	100.0%
		% within Outcome	18.9%	25.8%	.0%	23.0%
	51-60	Count	5	8	0	13
		% within Age Group in years	38.5%	61.5%	.0%	100.0%
		% within Outcome	13.5%	12.9%	.0%	13.0%
	> 60	Count	1	5	0	6
		% within Age Group in years	16.7%	83.3%	.0%	100.0%
		% within Outcome	2.7%	8.1%	.0%	6.0%
Total		Count	37	62	1	100
		% within Age Group in years	37.0%	62.0%	1.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4.261(a)	8	.833
Likelihood Ratio	4.576	8	.802
Linear-by-Linear Association	.472	1	.492
N of Valid Cases	100		

Figure 10: Distribution of outcome of ADRs in different Age Groups



All age groups patient were mostly in the recovery phase. No statistical significant difference between age and outcome as the P value= .833.

GENDER VERSUS SERIOUSNESS OF REACTION

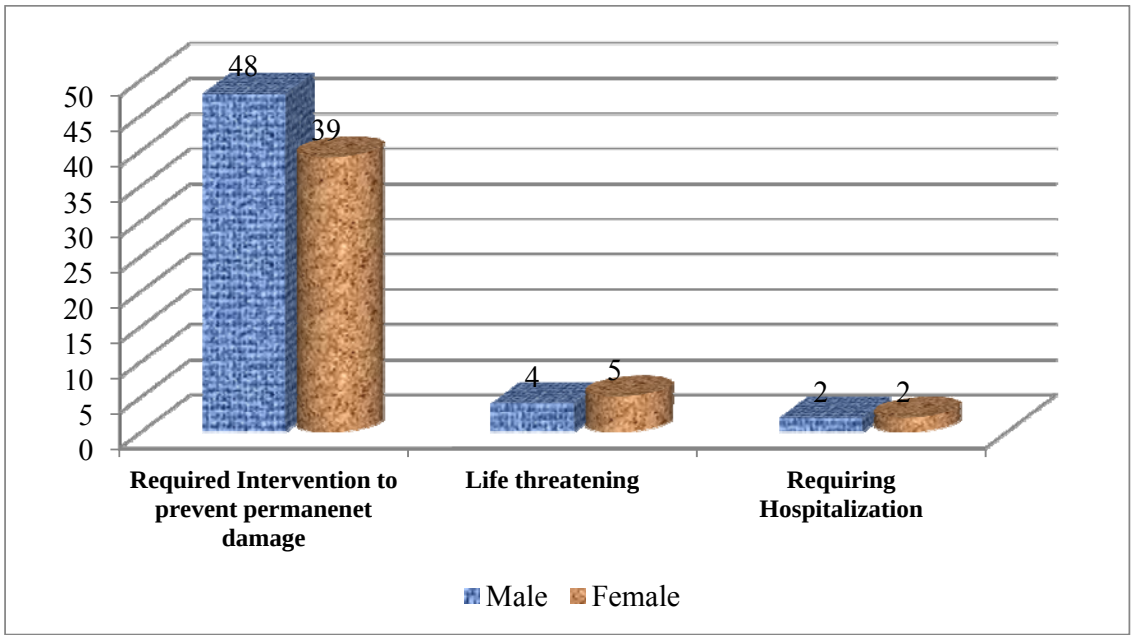
Table 14: Distribution of Gender versus Seriousness of Reaction

			Seriousness of Reaction			Total
			Required Intervention to prevent permanenet damage	Life threatening	Requiring Hospitali-zation	
Sex	Male	Count	48	4	2	54
		% within Sex	88.9%	7.4%	3.7%	100.0 %
		% within Seriousness of Reaction	55.2%	44.4%	50.0%	54.0%
	Female	Count	39	5	2	46
		% within Sex	84.8%	10.9%	4.3%	100.0 %
		% within Seriousness of Reaction	44.8%	55.6%	50.0%	46.0%
Total		Count	87	9	4	100
		% within Sex	87.0%	9.0%	4.0%	100.0 %
		% within Seriousness of Reaction	100.0%	100.0%	100.0%	100.0 %

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.405(a)	2	.817
Likelihood Ratio	.403	2	.817
Linear-by-Linear Association	.251	1	.616
N of Valid Cases	100		

Figure 11: Distribution of Gender versus Seriousness of Reaction



The seriousness of reaction was mostly similar in both sexes. There is no significant difference between sex and seriousness of reaction as the p value=.817 found by using Chi-square test.

GENDER VERSUS OUTCOME

Table 15: Distribution of Gender versus Outcome

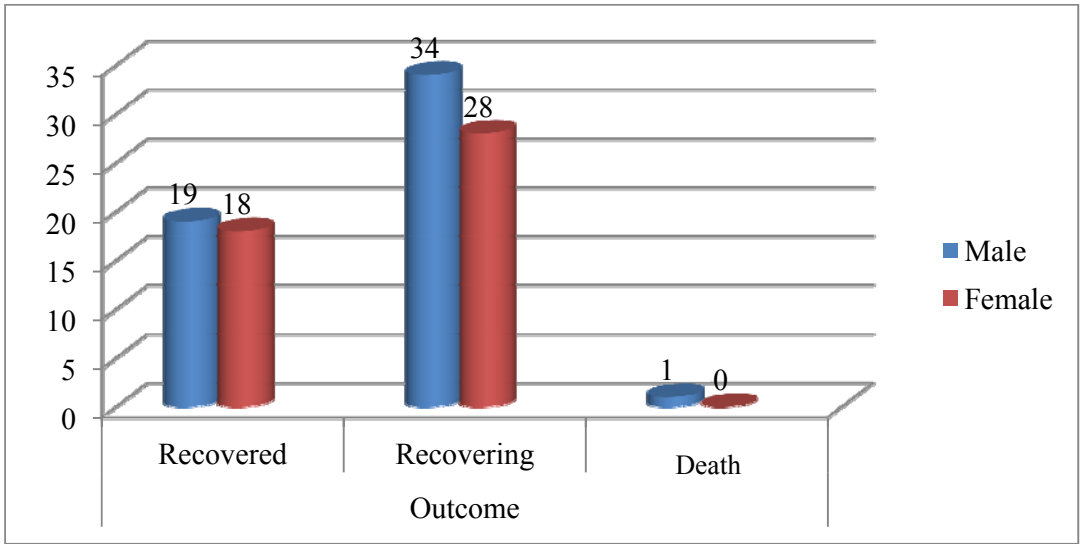
			Outcome			Total
			Recovered	Recovering	Death	
Sex	Male	Count	19	34	1	54
		% within Sex	35.2%	63.0%	1.9%	100.0%
		% within Outcome	51.4%	54.8%	100.0%	54.0%
	Female	Count	18	28	0	46
		% within Sex	39.1%	60.9%	.0%	100.0%
		% within Outcome	48.6%	45.2%	.0%	46.0%
Total		Count	37	62	1	100
		% within Sex	37.0%	62.0%	1.0%	100.0%
		% within Outcome	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.974(a)	2	.614
Likelihood Ratio	1.354	2	.508
Linear-by-Linear Association	.330	1	.566
N of Valid Cases	100		

.

Figure 12: Distribution of Gender versus Outcome



One male patient died due to ADR .There is no statistical difference between sex and outcome. By using Chi-square test the p value = .614 which is not significant statistically.

Concomitant medications versus seriousness of reaction

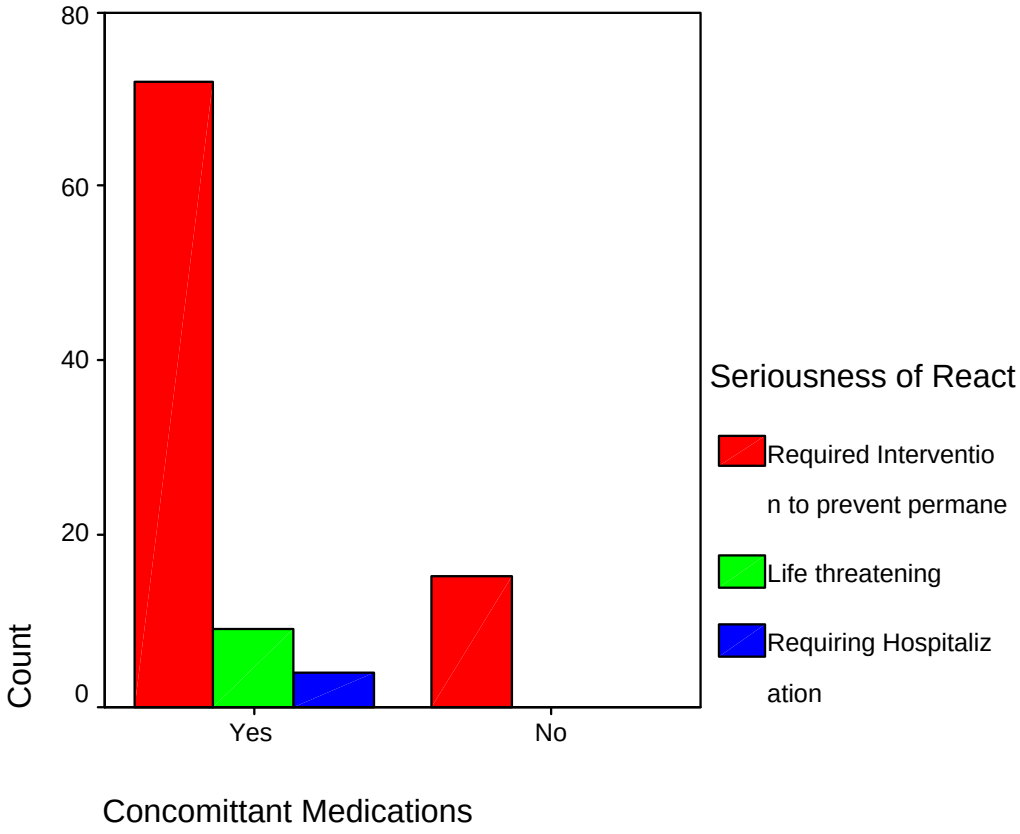
Table 16: Distribution of Concomitant Medications versus Seriousness of Reaction

Concomitant Medications			Seriousness of Reaction			Total
			Required Intervention to prevent permanent damage	Life threatening	Requiring Hospitalization	
	Yes	Count	72	9	4	85
		% within Concomitant Medications	84.7%	10.6%	4.7%	100.0%
		% within Seriousness of Reaction	82.8%	100.0%	100.0%	85.0%
	No	Count	15	0	0	15
		% within Concomitant Medications	100.0%	.0%	.0%	100.0%
		% within Seriousness of Reaction	17.2%	.0%	.0%	15.0%
Total		Count	87	9	4	100
		% within Concomitant Medications	87.0%	9.0%	4.0%	100.0%
		% within Seriousness of Reaction	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.637(a)	2	.268
Likelihood Ratio	4.555	2	.103
Linear-by-Linear Association	2.284	1	.131
N of Valid Cases	100		

Figure 13: Distribution of Concomitant Medications versus Seriousness of Reaction



The seriousness of reaction (85%) was found to be more when concomitant medications were used. There is no statistical significant difference between seriousness of reaction and concomitant medications used as the p value =.268 found by using Chi-square test.

DRUG REACTION VERSUS OUTCOME

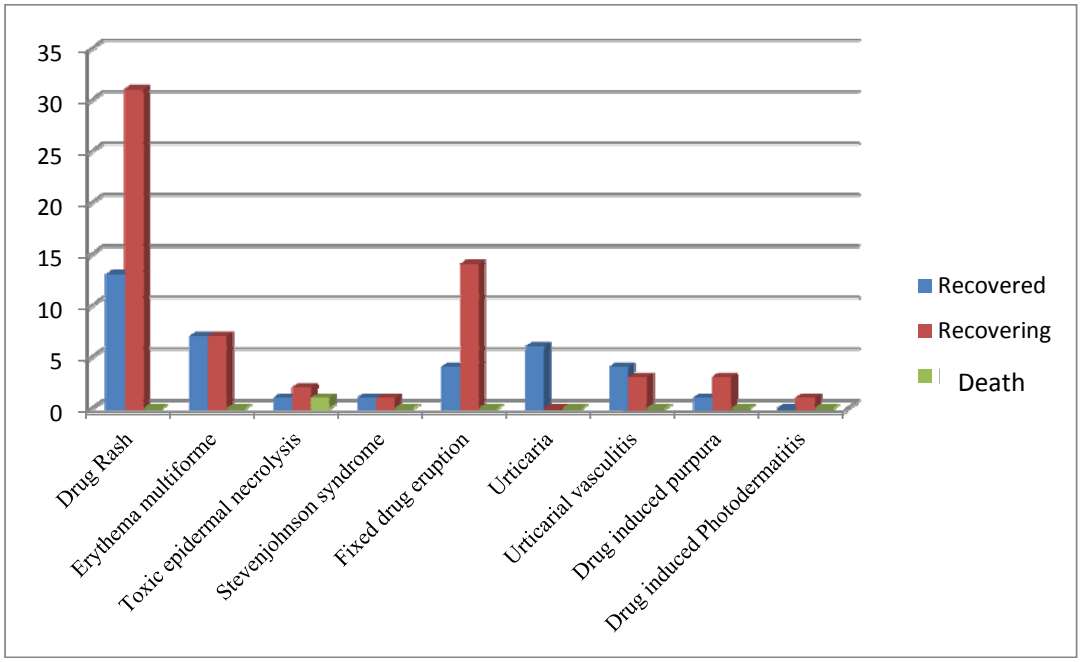
Table 17: Distribution of Drug Reaction versus Outcome

	Outcome			Total
Drug Reaction	**Recovered**	**Recovering**	**Death**	
Drug Rash	13	31	0	44
Erythema multiforme	7	7	0	14
Toxic epidermal necrolysis	1	2	1	4
Steven-johnson syndrome	1	1	0	2
Fixed drug eruption	4	14	0	18
Urticaria	6	0	0	6
Urticarial vasculitis	4	3	0	7
Drug induced purpura	1	3	0	4
Drug induced Photodermatitis	0	1	0	1
Total	37	62	1	100

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	40.509(a)	16	.001
Likelihood Ratio	25.021	16	.069
Linear-by-Linear Association	1.027	1	.311
N of Valid Cases	100		

Figure 14: Distribution of Drug Reaction versus Outcome



Fatality (1%) was seen among patients with toxic epidermal necrolysis (4%) whereas all types of skin reactions were mostly in recovering phase. There is no statistical significance between type of reaction and outcome of ADR.

Drug reaction versus Age group

Table 18: Distribution of different types of drug reaction versus Age group

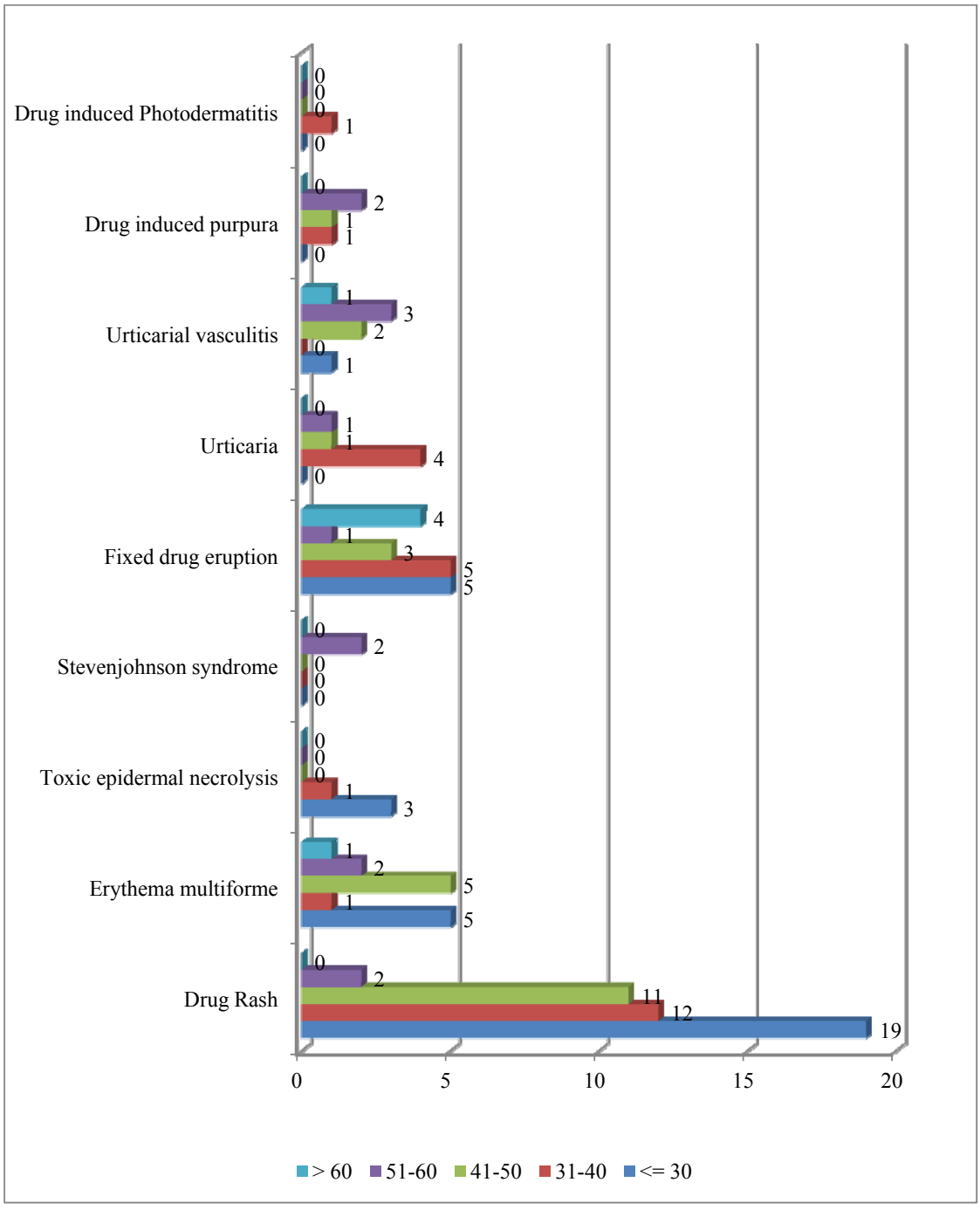
	Age Group in years					Total
Type of drug reaction	<= 30	31-40	41-50	51-60	> 60	
Drug Rash	19	12	11	2	0	44
Erythema multiforme	5	1	5	2	1	14
Toxic epidermal necrolysis	3	1	0	0	0	4
Stevenjohnson syndrome	0	0	0	2	0	2
Fixed drug eruption	5	5	3	1	4	18
Urticaria	0	4	1	1	0	6
Urticarial vasculitis	1	0	2	3	1	7
Drug induced purpura	0	1	1	2	0	4
Drug induced Photodermatitis	0	1	0	0	0	1
Total	33	25	23	13	6	100

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	59.482(a)	32	.002
Likelihood Ratio	56.722	32	.005
Linear-by-Linear Association	11.705	1	.001
N of Valid Cases	100		

Drug rash was most common in the age group of ≤ 30 years (19%). Steven-Johnson syndrome (2%) was seen only in the age group 51-60 years. There is statistical significance between age and drug reaction as the p value =.002 by Chi-Square test.

Figure 15: Distribution of different types of drug reaction versus Age group



DIFFERENT TYPES OF DRUG INDUCED SKIN REACTION VERSUS GENDER

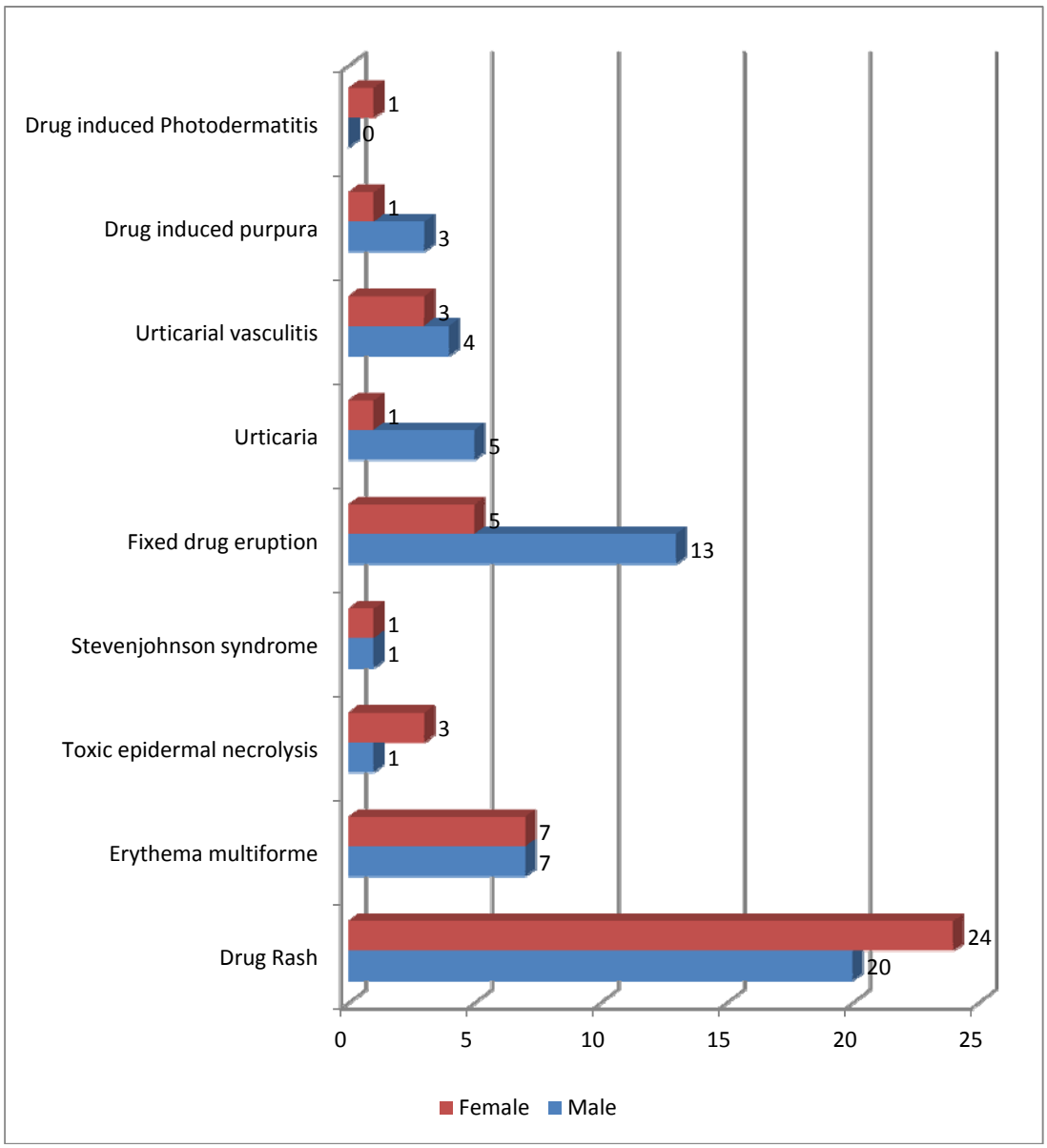
Table 19: Distribution of different types of drug reaction versus gender

	Sex		Total
Type of drug reaction	Male	Female	
Drug Rash	20	24	44
Erythema multiforme	7	7	14
Toxic epidermal necrolysis	1	3	4
Steven-johnson syndrome	1	1	2
Fixed drug eruption	13	5	18
Urticaria	5	1	6
Urticarial vasculitis	4	3	7
Drug induced purpura	3	1	4
Drug induced Photodermatitis	0	1	1
Total	54	46	100

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.147(a)	8	.330
Likelihood Ratio	9.940	8	.269
Linear-by-Linear Association	3.313	1	.069
N of Valid Cases	100		

Figure 16 : Distribution of different types of drug reaction versus gender



Drug rash was most common in females (54.5%) than males (45.5%). Steven Johnson Syndrome and Erythema Multiforme has equal distribution. Other reactions were distributed more in Males. There was no statistical difference between sex and drug reaction. The p value =.330 is not statistically significant found by using Chi-Square test.

SUSPECTED DRUG VERSUS AGE GROUP

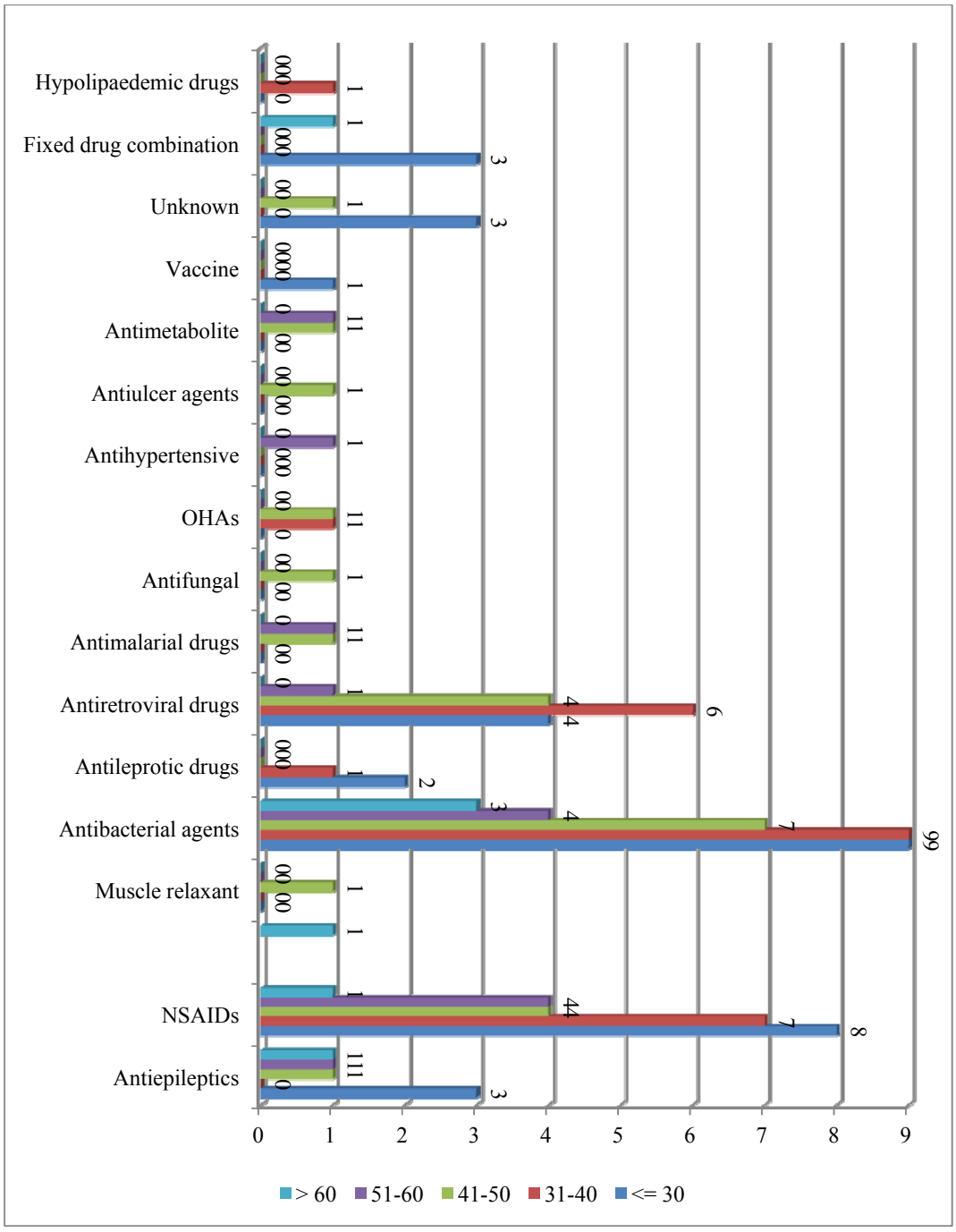
Table 20: Distribution of Suspected Drug causing reaction versus Age Group in years

	Age Group in years					Total
Suspected Drug	<= 30	31-40	41-50	51-60	> 60	
Antiepileptics	3	0	1	1	1	6
NSAIDs	8	7	4	4	1	24
Muscle relaxant	0	0	1	0	0	1
Antibacterial agents	9	9	7	4	3	32
Antileprotic drugs	2	1	0	0	0	3
Antiretroviral drugs	4	6	4	1	0	15
Antimalarial drugs	0	0	1	1	0	2
Antifungal	0	0	1	0	0	1
OHAs	0	1	1	0	0	2
Antihypertensive	0	0	0	1	0	1
Antiulcer agents	0	0	1	0	0	1
Antimetabolite	0	0	1	1	0	2
Vaccine	1	0	0	0	0	1
Unknown	3	0	1	0	0	4
Fixed drug combination	3	0	0	0	1	4
Hypolipaedemic drugs	0	1	0	0	0	1
Total	33	25	23	13	6	100

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	53.512(a)	60	.710
Likelihood Ratio	55.661	60	.635
Linear-by-Linear Association	.421	1	.517
N of Valid Cases	100		

Figure 17: Distribution of Suspected Drug causing reaction versus Age Group in years



There is no significant difference between suspected drug causing reaction and age.

SUSPECTED DRUG VERSUS GENDER

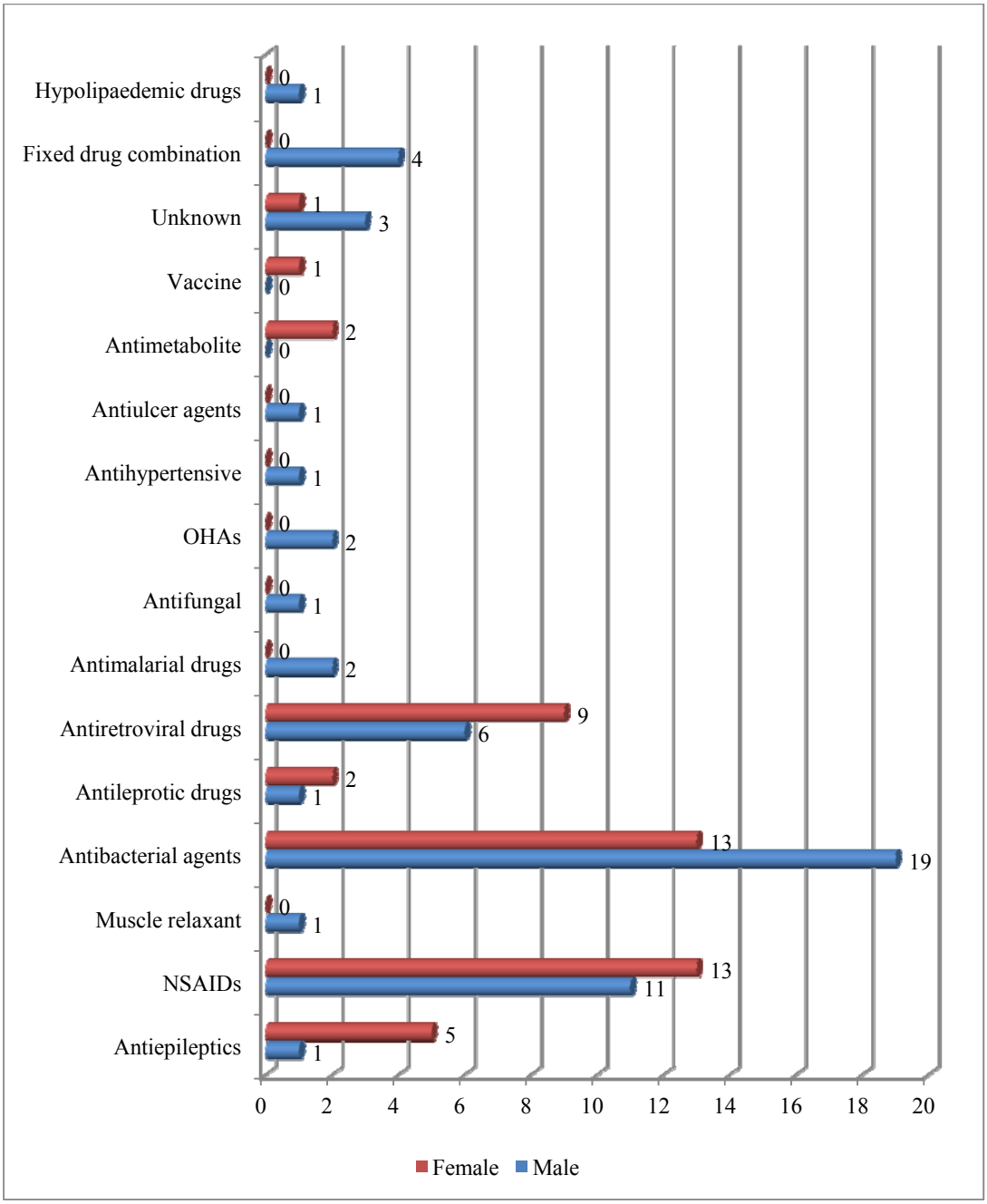
Table 21: Association of Suspected Drug versus Gender

Suspected drug		Sex		Total
		Male	Female	
	Antiepileptics	1	5	6
	NSAIDs	11	13	24
	Muscle relaxant	1	0	1
	Antibacterial agents	19	13	32
	Antileprotic drugs	1	2	3
	Antiretroviral drugs	6	9	15
	Antimalarial drugs	2	0	2
	Antifungal	1	0	1
	OHAs	2	0	2
	Antihypertensive	1	0	1
	Antiulcer agents	1	0	1
	Antimetabolite	0	2	2
	Vaccine	0	1	1
	Unknown	3	1	4
	Fixed drug combination	4	0	4
	Hypolipaedemic drugs	1	0	1
Total		**54**	**46**	**100**

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	21.389(a)	15	.125
Likelihood Ratio	27.740	15	.023
Linear-by-Linear Association	4.340	1	.037
N of Valid Cases	100		

Figure 18: Association of Suspected Drug versus Gender



Females were affected more by Antiepileptics (5), NSAIDs (13), Antiretroviral drugs (9) and Antimetabolite (2). Antibacterial (19), Fixed drug combinations (4%), have affected more males. There is no significant difference between drug groups and sex as the p value = .125.

DISCUSSION

AGE

Table 1 and Figure 1 show that 33% of drug induced- skin reaction was common in the age group ≤ 30 years. 25 % of ADRs were seen in 31-40 years followed by 23 % in 41-50 years and 13 % in 51-60 years. About 6 % of ADR was seen above 60 years. Hence the age group more commonly affected was ≤ 30 years.

Sushma et al in their study found that drug induced skin reactions were mostly seen in third and fourth decades of life.[59] In our study more reaction were seen in the age group≤ 30 years. Hence more caution should be taken while prescribing medicines to this age group.

GENDER

Table 2 and Figure 2 show that Drug induced- skin reactions were found more in males (54%) compared to females (46%).However it is not statistically significant. But both genders are vulnerable.

Mahmood Farshchian et al studied 308 patients with adverse cutaneous drug reaction from 2007–2009 and found that Females (63%) were more commonly affected than males (37%).[60] In our study males (54%) were more affected than females(46%) but statistically not significant.

ONSET OF REACTION

Table 3 shows the time interval between the drug intake and onset of adverse reaction. On the day of drug intake 13% were affected by drug induced

skin reactions. More number of cases was affected after 24 hours. The inference from this was that in sensitized patients the reactions starts earlier. The frequency of cases decreased as the time progresses but still the reaction has occurred. Even after 4 weeks interval the drug reactions occurred and was caused by antiretroviral drugs. Hence physician should be alert upto three weeks.

ADVERSE DRUG REACTION

Table 4 and Figure 3 show the profile of drug induced -skin reactions. Most common drug induced skin reactions was Drug Rash (44%) followed by Fixed drug eruption (18%) and Erythema Multiforme (14 %). Less than 10 % lesions were Toxic epidermal necrolysis (4%), Steven Johnson Syndrome (2%), Utricaria (6%) and Urticarial Vasculitis (7%). Less than 5% lesions were Drug induced purpura (4%) and Drug induced Photo dermatitis (1%).

Mahmood Farshchian et al studied 308 patients with adverse cutaneous drug reaction from 2007–2009 and found that Acute urticaria was the most common clinical presentation (59.2%) followed by fixed drug eruptions (18.5%), and maculopapular eruptions (14.9%).[60]

Noel, et al found that drug rash was the common the most common type of cutaneous drug reaction.[6] Study performed by Souissi et al in 2007, found that the most common cutaneous clinical manifestation was maculopapular eruption followed by fixed drug eruptions, and antibiotics and NSAIDs were the most commonly causing agents.[63] Results of this study were comparably similar to the studies of Noel and Souissi et al.

Table 17 and Figure 14 show the distribution of drug reactions versus their outcomes. Out of 4 cases of toxic epidermal necrolysis one patient died. All other types of skin reactions were mostly in recovering phase. There is no statistical significance between type of reaction and outcome.

Table 18 and figure 15 shows the distribution of different types of drug reactions versus age group. Drug rash was most common in the age group of $\leq$ 30 years (19%). Steven Johnson Syndrome (2%) was seen only in the age group 51-60 years. Exact mechanism for this is not known. There is statistical significance between age and drug reaction as the p value =.002 by Chi-Square test.

Study of 464 case series reported by Kauppinen K found that 4% patients had Steven Johnson Syndrome.[64] In our study 2% of patients had Steven Johnson Syndrome.

Table 19 and Figure 16 show the distribution pattern of different type of drug reactions versus genders. Drug rash was more common in females (54.5%) than males (45.5%). Steven Johnson Syndrome and erythema multiforme have equal distribution between both genders. Other reactions were distributed more in males. However there was no statistical difference between sex and type of drug induced skin reaction. The p value =.330 is not statistically significant found by using Chi-Square test.

SUSPECTED DRUG

Table 5 and Figure 4 show the frequency of various group of drugs suspected to be the causative agents. Antibacterial agents (32%) were the most common agents causing drug induced skin reaction followed by NSAIDs (24%) and antiretroviral agents (15%). 4 % of drug eruptions were caused by fixed drug combinations. 4 % of lesions were caused by unknown drugs were the patient was unable give details about the drug taken. Muscle relaxant, Antifungal, Antihypertensive, Antiulcer, and Vaccine has caused 1 % of reaction individually.

Mahmood Farshchian et al studied 308 patients with adverse cutaneous drug reaction from 2007–2009 and found that Beta-lactam antibiotics was found to be the most frequent cause of adverse cutaneous drug reactions (42.7%), followed by non-steroidal anti-inflammatory drugs (16.5%).[60]

Ghosh, et al in Manipal found that Antimicrobials were the most common group causing cutaneous drug reaction.[61] In our study also antibacterial agents have caused more drug induced skin reactions which was comparably similar to the above studies.

Table 20 and figure 17 show the distribution of suspected drug causing reaction versus age group. Antiepileptics (3), NSAIDs (8), Antibacterial agents (9) Antileprotics (2), Vaccine (1) caused drug reactions more in the age group $\leq$ 30 years. Antimetabolites and Antimalarials caused reaction in the age group 51-60 years and > 60 years. There is no significant difference between suspected drug causing reaction and age. By using Chi-square test the p value=.710 which is not statistically significant.

Table 21 and Figure 18 show the association of suspected drug versus gender. Females were affected more by Antiepileptics (5), NSAIDs (13), Antiretroviral drugs (9) and Antimetabolite (2). Other groups of drugs like Antibacterial (19), Fixed drug combinations (4%), have affected more males compared to females. There is no significant difference between drug groups and gender. The p value = .125 assessed by Chi-Square test is not statistically significant.

Suspected drugs that caused drug reaction were 1) Antibacterial agents - Amoxicillin, Ampicillin, Co-trimaxazole, Doxycycline, Tetracycline, Ciprofloxacin, Levofloxacin, Ofloxacin, Cefixime, Vancomycin. 2) Antitubercular drug - Pyrazinamide, 3) Antileprotic drug - Dapsone 4) Antifungal – Griseofulvin 5) Antiretroviral drugs - Nevirapine and Efavirenz 6) Antimalarial - Artesunate, Primaquine 6) NSAIDs – Diclofenac, Aceclofenac, Nimuselide, Prophiphenazone and Piroxicam. 7) Muscle relaxant - Thiocolchicoside, 8) Antiepileptics - Carbamazepine, and Phenytoin. 9) H_2 blocker - Ranitidine 10) Oral hypoglycemic agent - Glibenclamide and Metformin. 11) Antihypertensive - Atenolol, 12) Antimetabolite - Methotrexate 13) Vaccine - Antirabies vaccine, 14) Hypolipidaemic drug- Rosuvastatin.

Oral route (96%) was the most common route of drug administration whereas parenteral route of administration was found only in 4% of cases. All drugs were given in appropriate doses except in cases where the drug history was not known.

CONCOMITTANT MEDICATIONS AND CO-MORBIDITIES

Table 6 and Figure 5 show that Concomitant medications were used in 85% of Cases. The medications were used for co-morbidities like hypertension, hypothyroidism, diabetes mellitus, AIDS, seizure disorder, bronchial asthma, cardiac disorders, postpartum sepsis, brain tuberculoma, post surgical sepsis, tuberculosis, leprosy, systemic lupus erythematosus, burns, and prostate enlargement. Hence polypharmacy may have increased the incidence of ADRs.

An Australian study done by Stanton et al showed that 4.4% of all adverse drug reactions resulting in hospital admission were due to drug interactions.[27] In our study since concomitant medications were also used drug interaction could also have played a role in causing drug reaction. This has to be researched in future.

LAB DETAILS

Laboratory investigations pertaining to the ADR- Drug induced purpura was done to rule out hematological disorders and also for severe reactions. Laboratory investigations were also done for co-morbidities.

SERIOUSNESS OF REACTION

Table 7 and Figure 6 show the seriousness of adverse drug reactions. All cases required interventions in the form of stopping the drug, symptomatic management and hospitalization for severe reactions. 87 % of cases required intervention to prevent permanent damage and were managed without

hospitalization. 4% of cases were hospitalized in the dermatology ward for management. 9% of cases were life threatening required intensive care monitoring.

Table 12 and Figure 9 Shows that the all ADRs required intervention in all age groups.

Table 14 and figure 11 show that the seriousness of reaction was mostly similar in both sexes. There is no significant difference between sex and seriousness of reaction as the p value=.817 found by using Chi square test.

Table 16 and figure 13 show the distribution of concomitant medications and seriousness of reaction. The seriousness of reaction (85%) was found to be more when concomitant medications were used. There is no statistical significant difference between seriousness of reaction and concomitant medications used as the p value =.268 found by using Chi-Square test.

OUTCOME

Table 8 and Figure 7 show the outcome of drug induced skin reaction. 37 cases recovered. 62 cases were in recovery phase as per the CDSCO Suspected adverse drug reaction form report. One case died due to severe life threatening serious drug reaction. History of drug allergy was present in that case which could have been prevented.

Table 13 and Figure 10 show that maximum numbers of patients were recovering in all ages. The patient who died due to severe ADR belongs to the age group $\leq$ 30 years.

Table 14 and figure 11 show that the seriousness of reaction was mostly similar in both genders. The admission rate was similar in both genders (Female -7% and Male- 6). There is no Significant difference between gender and seriousness of reaction as the p value = .817 found by using Chi square test.

Table 15 and figure 12 show the distribution of Gender versus Outcome. One male Patient died due to ADR .There is no statistical difference between gender and outcome. By using Chi-square Test the p value = .614 which is not significant statistically.

CAUSALITY ASSESSMENT

Table 9 and Figure 8 show the Causality Assessment by using WHO causality assessment Scale. 52 ADRs were Probable, 44 ADRs were Possible and only 4 reactions were Certain.

Sachin Hiware et al study shows the causality assessment by WHO causality assessment scale for 872 CDRs. The period of study was from june 2005 to may 2009. It was found to have 580 certain, 260 probable and 32 possible CDRs.[65] In our study 100 ADRs were analyzed and the Causality assessment of ADR done by WHO assessment scale revealed that 52 ADRs were Probable, 44 ADRs were Possible and 4 ADRs were Certain. Only 4 ADRs were certain as rechallenge was not done.

Table 10 shows the Causality assessment by using Naranjo algorithm. All ADRs were Probable with score of 6-7. 96 % of ADRs score was 6 and 4% of cases had previous history of drug allergy and the score was 7.

SEVERITY ASSESSMENT OF ADR

Severity assessment of ADR was done by using Modified Hartwig and Siegel Scale - 1992. Table 11 shows that 87 % of ADRs were moderate in severity. 9% of patients were hospitalized for severe ADR. Out of which 1 patient died due to severe Toxic epidermal necrolysis.

LIMITATIONS OF THE STUDY

The study was done in a limited group of population. The concentration of drug in blood or other samples was not detected which may be helpful in preventing the toxic dose concentration. Rechallenge for drug reaction was not performed in the study due to ethical consideration.

CONCLUSION

The study was undertaken to analyze the profile of drug induced skin reaction in Outpatient department of Dermatology and to assess the causality, severity and socio-demographic profile of adverse drug reaction. The sample size analyzed was 100. The aim and objectives were met. Most common age group affected belongs to $\leq$ 30 years. Men (56%) were more affected. Drug rash was the most common drug induced reaction. The suspected drug causing more number of reactions was antibacterial agents. 52 ADRs were probable, 44 ADRs were possible and 4 reactions were certain. Wi

thdrawal of drug along with symptomatic management has made complete reversal of drug reactions to normality except one drug reaction- Toxic epidermal necrolysis due to the suspected drug group NSAID which terminated fatally. Hence the study gives a representative view about the ADRs among patients attending dermatology O.P in a tertiary care hospital.

India is the fourth largest manufacturer of pharmaceutical products in the world and emerging as clinical trial hub. Hence constant vigilance in detecting ADRs is needed so that drug therapy is safe and effective. Possible preventive measures to reduce ADRs are 1) to avoid inappropriate use of drugs, 2) to use appropriate dose, route and frequency of drug administration based on patients variables, 3) previous history of drug reaction should be considered and 4) appropriate laboratory monitoring. 15-20 % of hospital budget is spent for the treatment of ADR.[66] Hence ADR database studies are conducted across

multiple centres through active collaboration with various specialists and pharmacologists which can provide early warning signals of drug reaction and widens Pharmacovigilance in India.

Hippocrates admonition “atleast no harm” should be followed by all Health care professionals.

BIBILIOGRAPHY

1. Harrisons Principles of Internal Medicine, 17th edition, Newyork: Mc Graw hill companies; 2008, 1:1.

2. Tripathi KD. Essentials of Medical Pharmacology. 7th ed. New Delhi: Jaypee brothers, 2013, 1:2.

3. World Health Organization-International drug monitoring 1972: the role of national centers. World Health Organ Tech Rep Ser 498:1-82

4. Breathnach SM. Adverse cutaneous reactions to drugs. Clin med 2002; 2:15-9.

5. Chosidow OM, Stern RS, Wintroub BU. Cutaneous drug reaction, In: Kasper DL, Braunwald, editor.

6. Commission on Anesthetics. Lancet, 1893; i: 629-38.

7. Wade OL.The dawn of concern. In: Adverse reactions to drugs: 1-10Acford Ltd, chicster 1970.

8. Randell T. Thalidomide's back in the news, but in more favorable circumstances .JAMA, 1990; 263:467-68.

9. Caranos GJ, May FE, Stewart RB, Cluff LE, Drug associated deaths of medical inpatients. Arch Intern Med 1976:136(8):872-875.

10. Einarson TR Drug related hospital admissions Ann pharmacotherapy 1993:27:832-40.2.

11. Bates DW, Boyle DL, villet MVV Schneider J, Leapse L. Relationship between medication errors and adverse drug events Gen Intern Medicine, 1995 a: 10:199-205.3.

12. Dhikav V, Singh S, Anand KS adverse drug reaction monitoring in India. J Ind Acad clin Med, 2004; 5(1):27-33.

13. Martys CR. Adverse reactions to drugs in general practice.Br Med J, 1979;2(6199):1194-1197.

14. Alanko K, Stubb S, Kauppinen K. Cutaneous drug reaction: clinical types and causative agents. A five year survey in Patients (1981-85). Acta Derm Venereol 1989; 69:223-6.

15. Harrison's principle of internal medicine, 16th edition, Newyork: Mc Graw hill companies; 2005 p.318.

16. Levine RR Factors modifying the effects of drugs in individuals. In: Pharmacology: drug actions and reactions. Boston (MA): Little Brown and Co.1973:261-9.

17. Dhikav V, Singh S, Anand KS adverse drug reaction monitoring in India. J Ind Acad clin Med, 2004; 5(1):27-33.

18. Philip J Gregory, Karen L Keir. Medication Misadventures: Adverse drug reaction Information: Aguide for Pharmacists' ed. Patrick Malone, McGraw Hill Professional, 2000:487-518.

19. Post Approval Safety Data management: Definitions and standards for expedited reporting.ICH E2D.Current step 4 - version dated November 2003.

20. Stephen M D B, Talbot J C C and Routledge P A, The detection of new adverse drug reactions. Basinstoke, Macmillan Publishers Ltd, UK, Ed. (1998), 546pp.

21. Hunziker, et al. 1997 "Comprehensive hospital drug monitoring (CHDM): adverse skin reactions 20 year survey." Allergy, 52:388-393.

22. http://www.who-umc.org/(last accessed on April 9, 2015

23. Boley SJ, Allen AC, Schults L, Schwarts S. Potassium induced lesions of the small bowel. I. Clinical aspects. JAMA 1965; 193:997-1000.

24. Nelson SD. Molecular mechanism of hepatotoxicity caused by acetaminophen. Semen Liver Dis, 1990; 10:267-278.

25. Kalow W Pharmacogenetics: Heredity and the response to drugs. Saunders .Philadelphia.1962.

26. D'Arcy PF Epidemiological aspects of iatrogenic disease .In:D'ArcyPF, Griffin JP, eds, Iatrogenic Diseases. Oxford University press, 1986; 29-58.

27. Stanton LA, Peterson GM, Rumble RH, Cooper GM, Polack AE. Drug related admissions to an Australian Hospital. J Clin Pharm Ther 1994; 19:341-347.

28. Brodie M, Feely J .Adverse drug interaction. In; Feely J, ed., New drugs.London: BMJ, pp.29-39.

29. Fromm MF, Kim RB, Stein CM, Wilkinson GR, Roden DM .Inhibition of P-glycoprotein-mediated drug transport: A Unifying mechanism to explain the interaction between digoxin and quinidine.circulation, 1999; 99(4):472-474.

30. Katzung BG, Masters SB, Trevor AJ (Eds): Basic and Clinical Pharmacology:12th edn: Lange medical book, Tata McGraw-Hill, New Delhi, 2012, 5: 71

31. Tripathi KD. Essentials of Medical Pharmacology. 7th ed. New Delhi: Jaypee brothers, 2013 , 5:79

32. Sharma HL, Sharma KK, Principles of Pharmacology: 2nd edn; Paras Medical Publisher, Hyderabad, 2011, 8: 98.

33. Goodman & Gilman's The Pharmacological Basis of Therapeutics -12th edition, Mc Graw Hill, 2011, 1:8.

34. LamarqueV, PletanY. The Pharmaceutical industry and the adverse effects of the drugs. Ann Pharm Fr.2007; 65(5):308-14.

35. Hartzema AG, Porta MS, Tilson H.Introduction to pharmacoepidemiology.Drug Intelligence and Clinical Pharmacy 1987; 21:739-40.

36. ICH Guidance E2D; Post approval Safety Data Management: Definitions and standards for expedited reporting. November 2003.

37. Thakrar BT, Grundschober SB, Dossegger L. Detecting signals of drug –drug interactions in a spontaneous reports database.Br J Cin Pharmacology 2007;64(4):489-95.

38. Theissard F, Roux E, Miremont-Salame G, Fourrier-Reglat A, Haramburu F, Tubert-Bitter P, Begaud B. Trends in spontaneous adverse drug reaction

reports to French Pharmacovigilance system (1986-2001).Drug Saf 2005;28(8):731-40.

39. Inman W.H.W and Mustrin, WW Jaundice after repeated exposure to Halothane: An analysis of reports to the committee on safety of medicines.Br Med J 1974;1:5-10

40. Inman WHW, Vessy MP. Westerholm B and Engelind A. Thromboembolic disease and the steroidal content of oral contraceptives.Br Med J 1970;2:203

41. Adithan C. National Pharmacovigilance programme. Indian J Pharmacology 2005;37(6):347

42. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-Phentermine. New Engl J Med 1997; 337(9):581-88.

43. Zhou Y, Li N, Zuang M, Wu T, Yao X, Du L, Wei M, Wu X. Green tea consumption and gastric cancer risk: meta-analysis of epidemiologic studies. Asia Pac J Clin Nutr 2008; 17(1):159-65

44. Kennedy DL Mcinnis T. Monitoring adverse drug reactions: the FDA's new Medwatch program, P and T 1993, 833-4,839-42.

45. Roujeau JC, Stern RS: Severe adverse cutaneous reactions to drugs Eng J Med 1994; 331:1272.

46. Curtsinger J M, Schmidt C S, Mondino A, et al. Inflammatory cytokines provide a third signal for activation of native CD4+ and CD8+ Tcells.J Immunol 1999,162:3256-3262.

47. Sehgal VH, Gangwani OP: Genital fixed eruptions, Genitourin Med 1986;62:56

48. Pelicano R et al:Familial occurrence of fixed drug eruption,Acta Derm Venereol 1992;72:292

49. Gafoor PM, George WM: Fixed drug eruptions occurring on the male genitals, Cutis 1990:45:242

50. Lawley T, Bielory L, Gascon P, et al. A prospective clinical and immunologic analysis of patients with serum sickness. Eng J Med 1984; 311:1407-13.

51. Breathnach S.M. Erythema Multiforme, Steven-johnson syndrome and toxic epidermal necrolysis.In: Rooks textbook of dermatology 8th Edn. Burns T, Breathnach S, Cox N,Griffiths C ,ed. Blackwell Publishing;2010:76.1-76.22

52. Lerner LH, Qureshi A, Reddy BV, Lerner E A. Nitric acid synthase in toxic epidermal necrolysis and Steven-Johnson Syndrome. Invest Dermatol 2000:114:196-199.

53. Lehr M, Picheler WJ. The immunological and clinical spectrum of delayed drug induced exanthems.Curr Opin Allergy Clin Immunol.2004;4:411-419

54. Syed Ahmed Zaki. Adverse drug reaction and causality assessment scales. Lung India. 2011 Apr-Jun; 23(2): 152-153. PMCID: PMC3109846

55. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther.1981; 30:239-45.

56. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am j Hosp Pharm. 1992;49:2229-32

57. Protocol for National Pharmacovigilance Program, CDSCO, Ministry of Health and Family welfare, Government of India November 2004.

58. Edward R, Aranson JK, Adverse drug reactions: Definitions, diagnosis and management .Lancet 2000; 356:1255-9.

59. Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse cutaneous drug: a 9 year study from a South Indian Hospital. Pharmacoepidemiology Drug Saf. 2005; 14(8):567–570.

60. Mahmood Farshchian et al ,Clinical, Cosmetic and Investigational Dermatology 2015:8 53–56)

61. (Ghosh S, Leelavathi D, Padma GM Rao. Study and evaluation of the various cutaneous adverse drug reactions in Kasturba Hospital, Manipal. Indian J Pharma Sci March 2006:68:212)

62. Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care centre. Indian J Pharmacology 2004:36:292-5

63. Souissi A, Fenniche S, Benmously R, Ben JS, Marrak H, Mokhtar I. Study of the cutaneous drugs reactions in a teaching hospital in Tunis. Tunis Med 2007; 85(12):1011–1015.

64. Kappinen K. Drug eruptions: A series of 464 cases in the dermatology, university of Turku, Finland during 1966-1970.Acta Allergol 1972; 24:407.

65. Sachin Hiware et al, Evaluation of Cutaneous Drug Reactions in Patients Visiting Out Patient Departments of Indira Gandhi Government Medical College and Hospital (IGGMC and H), Nagpur. Indian Journal of Dermatology 2013; 58(1):18-21.

66. Field TS, Gilman BH, Subramanian S, et al. (2005) The costs associated with adverse drug events among older adults in the ambulatory setting. Med Care 43; 1171-1176.

ANNEXURE A

PATIENT DATA COLLECTION – PROFORMA

DEPARTMENT OF PHARMACOLOGY, KMC , CHENNAI.

1. DATE :

2. OP NO :

3. NAME :

4. AGE (yrs) :

5. GENDER :

6. HEIGHT(cm) :

7. WEIGHT(kg) :

8. ADDRESS :

9. OCCUPATION :

10. CONTACT NUMBER :

Complaints:

History of present illness:

Past history:

Personal history:

Family history:

Clinical Examination:

Investigations:

Diagnosis:

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO

Central Drugs Standard Control Organization

Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhavan, ITO, Kotla Road, New Delhi
www.cdsco.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique no.

A. Patient Information

1.Patient Initials	2.Age at time of Event or date of birth	3. Sex ☐M ☐F 4. Weight ____Kgs
_____	----------	

12. Relevant tests / laboratory data with dates

B .Suspected Adverse Reaction

5. Date of reaction stated (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction

- ☐ Death (dd/mm/yyy)____
- ☐ Life threatening
- ☐ Hospitalization-initial or prolonged
- ☐ Disability
- ☐ Congenitial anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

15. Outcomes

- ☐ Fatal
- ☐ Continuing
- ☐ Recovering
- ☐ Recovered
- ☐ Unknown
- ☐ Other (specify)____

C.Suspected medication(s)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										

Sl.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address :_____

_____

Pin code : _____ E-mail _____

Tel. No. (with STD code): _____

Occupation _____Signature _____

17. Causality Assessment	18. Date of this report (dd/mm/yyyy)

ANNEXURE - B

INFORMED CONSENT FORM

Title of the study : Study of drug induced-skin reactions among patients attending outpatients department of dermatology.

Name of the participant : Age Sex :

IP No:

Name of the Principal investigator :

Name of the Institution : Department of Pharmacology, Kilpauk Medical College, Chennai – 600 010.

Documents of the informed consent

I_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am exercising my free power of choice, hereby give my consent to be included as a participant in **"**Study of drug induced-skin reactions among patients attending outpatients department of dermatology"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me
3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past including any native (alternative) Treatment.
6. I agree to cooperate with the investigator and I will inform her immediately if I suffer unusual symptoms.
7. I have not participated in any research study in the past
8. I am aware of the fact that I can opt out of the study at any time without having to given any reason and this will not affect my future treatment in this hospital.
9. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.
10. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
11. I have understood that my identity will be kept confidential if my data are publicly presented.
12. I have had my questions answered to my satisfaction.
13. I have decided to be in the research study.
14. I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information

given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Signature & Date

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம்:

ஆராய்ச்சி மையம்:

நோயாளியின் பெயர்: நோயாளியின் வயது:

பதிவு எண்:

நோயாளி கீழ்கண்டவற்றுள் கட்டங்களை (✔) செய்யவும்

1. மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன். ☐

2. மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிறேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன். ☐

3. ஆராய்ச்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக்கொள்ளலாம் என்றும், மேலும் இந்த நிபந்தனை நான் இவ்வாராய்ச்சியிலிருந்து விலகினாலும் தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டாது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கின்றேன். ☐

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் இந்த ஆராய்ச்சி காலம் முழுவதும் எனது உடல் நிலையில் ஏதேனும் மாற்றமோ அல்லது எதிர்பாராத பாதகமான விளைவோ எற்படுமாயின் உடனடியாக ஆராய்ச்சி குழுவினரை அணுகுவேன் என்றும் உறுதியளிக்கின்றேன். ☐

5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப் பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கின்றேன். ☐

6. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புருத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மத்திக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன். ☐

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை ஆராய்ச்சியாளரின் கையொப்பம்

இடம்: தேதி:

APPENDIX-C

WHO CAUSALITY ASSESSMENT SCALE FOR

SUSPECTED ADVERSE DRUG REACTIONS

(The Uppsala monitoring centre 2002)

Term	Description
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible(pharmacologically, pathologically) • Event definitive pharmacologically or phenomenological(i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality ,with reasonable time relationship to drug intake • Could not be explained by the disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or Laboratory test abnormality with a time to drug intake that makes a relationship improbable(but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ **Unclassified**	• Event or Laboratory abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

APPENDIX –D

CRITERIA FOR DETERMINING CAUSATIVE DRUG RELATIONSHIP TO ADVERSE DRUG REACTION (NARANJO ALGORITHM-1981)

The total score calculated from this table defines this category as: Possibly (Total Score 1-4) , Probably (Total Score 5-8) , Definitely (Total Score > 9)

Questions	Yes	No	Do Not Know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was given?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	
Did the adverse reaction appear when the drug was Re-administered?	+2	-1	0	
Are there alternative causes (other than the drug) that could have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+2	0	
Was the drug detected in blood (or other body fluid) in toxic concentrations?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the event confirmed by objective evidence?	+1	0	0	
Total score				

APPENDIX - E

ADR SEVERITY ASSESSMENT SCALE

Modified Hartwig and Siegel scale-1992

MILD

Level 1: An ADR occurred but required no change in treatment with the suspected drug.

Level 2: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay.

MODERATE

Level 3: The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and / or an antidote or other treatment was required. No increase in length of stay.

Level 4: Any level 3 ADR which increases length of stay by at least 1 day or the ADR was the reason for the admission.

SEVERE

Level 5: Any level 4 ADR which requires intensive medical care.

Level 6: The ADR caused permanent harm to the patient.

Level 7: The ADR either directly or indirectly led to the death of the patient.

FILE PICTURES OF DRUG INDUCED SKIN REACTIONS

Picture 1: Drug induced urticaria

Picture2&3: Drug induced rash

Fixed Drug Eruption (FDE)

Picture4: Bullous FDE

Picture5: FDE

Picture 6: Bullous FDE with erosion

Picture 7: Multiple FDE

TOXIC EPIDERMAL NECROLYSIS (TEN)

Picture 8

Picture 9: TEN with peeling

Picture10 &11: TEN with mucosal

Picture12: Erythema multiforme with target lesions

Picture13: Erythema multiforme with target lesions

Picture14: Steven Johnson syndrome

Picture15: Steven Johnson syndrome with palmar involvement

Picture 16: Urticarial vasculitis

Picture17 & 18: Photosensitive drug eruptions